FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

GENERAL AND PLASTIC SURGERY DEVICES PANEL

Friday,
January 30, 1998

Salons F and G
Gaithersburg Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland

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C O N T E N T S

P R O C E E D I N G S (8:45 a.m.)

MS. GANTT: Good morning, everyone. We're ready to begin this meeting of the General and Plastic Surgery Panel meeting. I'm Gail Gantt, the Executive Secretary of this panel and a reviewer in the Plastic and Reconstructive Surgery Devices Branch.

I remind everyone that you are requested to sign in on the attendance sheets which are available at the tables by the doors, and you may also pick up an agenda, panel meeting roster, and information regarding today's meeting here. The information includes how to find out about future meeting dates through the Advisory Panel phone line, which will list the tentative dates remaining for this year, and how to obtain meeting minutes or transcripts.

Before turning the meeting over to Dr. Morrow, I'm required to read two statements into the record, the deputization of temporary voting members statement, and the conflict of interest statement.

This is the appointment to temporary voting status. "Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990 and amended April 20, 1995, I appoint the following as voting members of the General and Plastic

Surgery Devices Panel for the duration of the meeting on January 30, 1998: Drs. Michelle Biros, Joseph Boykin, Phyllis Chang, Susan Galandiuk, John Howell, Janine Janosky, and Thomas Whalen.

"For the record, these persons are special government employees and are consultants to this panel or consultants and voting members of another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting."

Signed, "D. Bruce Burlington, M.D., Director, Center for Devices and Radiological Health, January 28, 1998."

The conflict of interest statement for the General and Plastic Surgery Devices Panel meeting, January 30, 1998. "The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety.

"To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the panel participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or

their employer's financial interest. However, the agency has determined that the participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the government.

"We would like to note for the record that the agency took into consideration other matters regarding Drs. Morrow and Joseph Boykin. These individuals reported other interests and/or financial interests in firms at issue, but on matters not related to topics being addressed by the panel. The agency has determined, therefore, that they may participate fully in discussions. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should exclude themselves from such involvement, and their exclusions will be noted for the record.

"With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they wish to comment upon."

Dr. Morrow?

DR. MORROW: Good morning. I'm Monica Morrow,

Professor of Surgery, Director of Breast Programs at Northwestern University in Chicago.

Today the panel will be making recommendations to the Food and Drug Administration on one premarket application.

The next item of business is to introduce the panel members who are giving of their time to help the FDA in these matters, as well as the FDA staff here at this table.

Beginning with Dr. Witten, could we please go around the table? State who you are, your specialty and position title, as well as status on the panel as a voting member, consumer representative, et cetera.

DR. WITTEN: I'm Dr. Witten, the Division Director of the Division of General and Restorative Devices at the FDA. I'm not a member of the panel but representing the FDA here.

DR. BOYKIN: Dr. Boykin. I'm a plastic surgeon, Medical Director of the Retreat Hospital Wound Healing Center, Assistant Professor of Plastic Surgery at the Medical College of Virginia at Richmond, and a voting member.

DR. GALANDIUK: Susan Galandiuk. I'm a colorectal surgeon. I'm an Associate Professor of Surgery

at the University of Louisville and a voting panel member.

DR. JANOSKY: Janine Janosky from the University of Pittsburgh School of Medicine, Department of Family Medicine and Clinical Epidemiology, Division of Biostatistics, and I'm a consultant to the panel.

MS. GANTT: I'm Gail Gantt, the executive secretary.

DR. BIROS: I'm Michelle Biros. I'm an emergency physician, and I practice at Hennepin County Medical Center in Minneapolis.

DR. WHALEN: Tom Whalen. I'm a pediatric surgeon, Associate Professor of Surgery and Pediatrics, Robert Wood Johnson Medical School, Camden, and voting member of the panel.

DR. CHANG: Phyllis Chang, Associate Professor, Section of Plastic Surgery at the University of Iowa in Iowa City, Iowa. I am a voting member of this panel.

DR. DUNCAN: Titus Duncan, Director of Minimally Invasive Surgery at the Medical College in Georgia at the Georgia Baptist Medical Center in Atlanta, Georgia. I'm a voting member.

DR. HOWELL: I'm John Howell, Chairman of Emergency Medicine at Georgetown University, and a voting member.

MS. BRINKMAN: I'm Maxine Brinkman, Director of Women's Services, Mercy Health Services in Mason City, Iowa. I'm a consumer representative and a non-voting member.

DR. BURNS: I'm Jim Burns, Vice President for Biomaterials and Surgical Products Research at Genzyme Corporation. I'm the industry representative for this panel and a non-voting member.

DR. MORROW: I would like to note for the record that the voting members present constitute a quorum as required by 21 CFR 14.

We will now proceed with the open public hearing session of this meeting. We have no one listed to speak at this time. Is there anyone in the audience who wishes to address the panel?

(No response.)

DR. MORROW: Seeing none, we will now proceed with the sponsor's presentation. I would like to remind the public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

We will now hear the PMA from Closure Medical on DermaBond.

MR. BAREFOOT: Good morning. My name is Joe Barefoot, and I am the Vice President of Quality Assurance and Regulatory Affairs at Closure Medical Corporation. I have the honor of leading the presentation of our PMA for DermaBond, a topical skin closure adhesive that will serve as a versatile alternative to sutures, staples, and strip-type adhesive wound closures. While topical skin closure adhesives have been in clinical usage elsewhere in the world, DermaBond represents the first such product to have progressed this far through the FDA review process and represents the most significant innovation in simple skin closure in the United States.

DermaBond is a sterile, liquid tissue adhesive containing a monomeric 2-octyl cyanoacrylate formulation, which I will refer to as 2-OCA. It is provided in a single-use applicator packaged in a blister pouch. The applicator is comprised of a crushable glass ampule contained within a plastic vial with attached applicator tip. As applied to the skin, the liquid adhesive is slightly more viscous than water. Upon contact with the skin, liquid DermaBond polymerizes to form a flexible, adhesive film to hold together the approximated wound edges.

Our clinical investigation was a prospective,

controlled, randomized study of over 800 subjects at 10 clinical sites that encompassed a spectrum of clinical specialties and settings. To our knowledge, it represents the largest, most comprehensive, and most rigorous study of any laceration or incision wound closure device. The study provided valid scientific evidence that DermaBond is a safe and effective skin closure device yielding good cosmetic results.

Accordingly, the indication being sought for DermaBond is: "DermaBond is intended for topical application to hold closed approximated wound edges of trauma-induced lacerations or surgical incisions, including punctures from minimally invasive surgery, that otherwise could be closed with sutures of U.S.P. size 5-0 caliber or smaller, staples, or adhesive strips."

I will begin the presentation with a description of the development of DermaBond. This will include a brief history of the development and use of tissue adhesives, followed by the chemical and polymerization characteristics of DermaBond and the preclinical testing performed on DermaBond.

Following me will be Dr. Dean Toriumi, Associate Professor in the Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology Head

and Neck Surgery, University of Illinois at Chicago. As a facial plastic surgeon, Dr. Toriumi participated as a clinical investigator in the DermaBond study. He will present the fundamental features of the study.

Following Dr. Toriumi will be Dr. Michael Thorn, Closure's consultant biostatistician who has extensive experience with both drug and device clinical studies. Dr. Thorn has participated in this project from the inception of the clinical protocol through the final analysis and study results. He will describe the statistical methods employed and report the statistical findings.

Following Dr. Thorn will be Dr. Judd Hollander, Clinical Research Director and Associate Professor in the Department of Emergency Medicine, University of Pennsylvania Medical Center in Philadelphia. As an emergency department physician, Dr. Hollander participated as a co-investigator in the DermaBond study while at his former institution, the Department of Emergency Medicine, State University of New York at Stony Brook. Dr. Hollander will discuss the cosmetic scale used in the DermaBond study and present his personal study experience with DermaBond, including its performance compared to other skin closure devices used in emergency medicine, drawing on insights

from an extensive, published wound registry he maintains.

Following Dr. Hollander, Dr. Toriumi will return to present his personal experience with DermaBond, including its performance compared to sutures in facial plastic surgery and the benefits for cosmetic surgery patients.

I will then present the conclusions and summary of the highlights of the DermaBond clinical study.

Following our presentation, we would be pleased to respond to any of your questions. Others who have played significant roles in product development and the clinical studies also are here today to help answer any of your questions. These include a clinical investigator who is a pediatrician and a specialist in pediatric emergency medicine, Dr. Thomas Bruns, as well as other consultants who are specialists in toxicology, regulatory affairs, and clinical affairs.

And now I will begin the technical and clinical portion of our presentation of the DermaBond PMA.

As I stated at the outset, DermaBond is a sterile formulation of 2-octyl cyanoacrylate, or 2-OCA. Upon polymerization, cyanoacrylates exhibit extraordinary adhesive properties. However, it is important to recognize the fact that not all cyanoacrylates are alike. The

biocompatibility and clinical performance of such products are affected by the homologue chosen, product formulation, manufacturing processes and controls, and applicator design.

Over the last several decades, short carbon chain or lower homologue cyanoacrylate products have been manufactured for both industrial and commercial uses. These include the widely used "Superglue," which is a methyl cyanoacrylate. The longer chain or higher homologue cyanoacrylates have been investigated as tissue adhesives in neurosurgery, ophthalmology, dentistry, skin wound closure, and aesthetic and reconstructive surgery. Overall, the clinical experience with topical skin closure adhesives of higher homologues of the cyanoacrylates is reported to have been very good, especially in the field of plastic surgery.

While initial uses of topical skin closure adhesives have been investigational in the U.S., clinicians elsewhere in the world have adopted them into their practice. Histoacryl is a butyl cyanoacrylate of another manufacturer used for topical closure in Europe and elsewhere outside the U.S. Butyl cyanoacrylate has a somewhat shorter carbon chain than 2-OCA. However, topical skin closure adhesives of any formulation are not currently

marketed in the U.S.

Closure has extensive experience in cyanoacrylate technology and has been successful in bringing other cyanoacrylate-based products into clinical study and practice in the U.S. An n-butyl formulation named NEXACRYL has undergone clinical study and is the subject of an approvable PMA for its intended use in ophthalmology as a protective sealant for corneal and scleral perforations. Also, a 2-octyl formulation similar to DermaBond, named OCTYLDENT, is the subject of a cleared Premarket Notification or 510(k) for its intended use in dentistry for cementing an NDA-approved drug impregnated fiber to periodontal tissue during treatment.

The main component of DermaBond is the 2-OCA monomer that comprises over 90 percent of the formulation. Other formulation components consist of polymerization inhibitors to control the transition from liquid formulation to solid polymer, a plasticizer to provide flexibility to the polymer film adhering to the skin, and stabilizers to prolong shelf life. D&C Violet is present to allow visualization of the monomer during application.

Please note the similarity of the DermaBond and Octyldent formulas on this slide. This will be relevant to a later slide.

Within approximately one minute of removal of the applicator tip from normally dry skin, DermaBond polymerizes and develops enough strength to hold the wound edges together without manual approximation. Some patients may experience a slight sensation of warmth associated with the heat of polymerization. Full mechanical strength of the adhesive film is achieved in approximately 2.5 minutes following application. Once formed as an adhesive film, DermaBond is flexible and provides continuous approximation of the wound edges for 5-10 days. DermaBond is not absorbed by the skin or underlying tissue. DermaBond sloughs from the wound as re-epithelization of the skin occurs, providing sufficient time for wound healing.

DermaBond was designed and developed specifically for use as a topical skin closure adhesive. The final product features the following design attributes:

DermaBond is a single use unit, and is packaged in a blister pack which permits presentation to a sterile field.

DermaBond is sterile and may be applied directly on the laceration or incision line for controlled application, as opposed to dropping or dripping it onto the wound.

It has a convenient set time, and forms a

strong and flexible polymer film.

I would like to switch from the slides for just a moment to show a short video of the DermaBond product being applied to a pig model. First, of course, the physician removes the DermaBond applicator from the blister pouch and holds the applicator away from the patient to prevent unintentional placement. Grasp the applicator with the thumb and a finger and apply pressure to the mid-point of the ampule to crush the inner glass ampule. Gently squeeze just sufficiently to express liquid adhesive to moisten the applicator tip.

The wound should be positioned horizontally. Manually approximate the wound edges using gloved fingers or forceps and apply a thin film of liquid using a gentle brushing motion.

Next we have a larger volume wound requiring a buried suture. This is followed by general layering of the DermaBond adhesive. A gentle brushing motion with a build of successive layers yields the best results.

This last scene demonstrates how strong and flexible DermaBond film is once it has polymerized. This is typical of what can be expected 2.5 minutes after completing the application of the adhesive.

The last attribute I wish to mention is

biocompatability. DermaBond was subjected to an extensive battery of toxicity tests to assure its biocompatibility. This slide shows the types of tests identified in ODE's biocompatibility guidance as relevant, along with the tests performed on DermaBond. You will note that Octyldent is listed on this slide also because of the high similarity between the Octyldent and DermaBond formulas. The biocompatibility data demonstrate that DermaBond poses no toxicological hazard to patients or users.

Three nonclinical studies were conducted to characterize and evaluate the wound closure attributes of DermaBond. These studies were conducted in juvenile pig and rat experimental models. The juvenile pig model was chosen because the animal's skin is similar to human skin with regard to skin closure properties. The rat model lent itself to accurate biomechanical measurements.

The purpose of the first study was to compare rates of wound dehiscence for DermaBond, Histoacryl, and 5-0 nylon sutures in the closing of skin incisions in the pig. Skin incisions were made on the backs of the animals. The incisions were closed either by suturing or by applying one of the two adhesives. Animals appeared normal throughout the observation period of ten days. Wound dehiscence was not observed in any incision closed with

DermaBond or sutures. Partial or complete dehiscence was observed in 7 of the 12 incisions closed with the shorter carbon chain or lower homologue adhesive, Histoacryl.

The purpose of this second study was to evaluate the biomechanical strength of wounds closed with DermaBond and currently marketed skin closure devices, and to perform histopathological evaluations of treated wound tissues. The biomechanical test measured strengths of wounds under tension at the point of failure. In this study, longitudinal skin full thickness incisions were made on the dorsolateral flank of the rat and then closed either by suturing with 5-0 nylon, by applying adhesive strips, or by applying DermaBond.

Groups of animals were observed for either 7 or 14 days. Animals from these groups were subjected either to biomechanical wound strength testing or to histopathological evaluation.

Incision wounds closed with DermaBond had wound strengths equal to those of sutures or adhesive strips at both the 7 and 14 days. The histopathological evaluation of the healing wounds and surrounding tissues revealed no adverse effects from DermaBond.

The purpose of the third study was to evaluate the biomechanical strength of wounds within one hour when

closed with DermaBond, under various application techniques or currently marketed devices. Multiple groups of rats were used to compare 5-0 and 6-0 nylon sutures, Histoacryl, and DermaBond when applied under conditions of minimal surface area, single-stroke application, and multiple stroke application. The animals were subjected to biomechanical wound strength testing at time intervals up to one hour after closure.

This biomechanical testing demonstrated that wounds closed with DermaBond were optimal when multiple strokes were applied. Wounds closed with DermaBond achieved, within 60 seconds, sufficient strength to hold the wound edges together without manual approximation, and reached full strength 2.5 minutes after application. DermaBond wound strengths at one hour were comparable to, but somewhat lower, than for sutures. Histoacryl had the lowest wound strengths.

These studies demonstrated that DermaBond in the animal models performs comparably with sutures and adhesive strips and warranted clinical evaluation.

At this time, I will turn the presentation over to Dr. Toriumi, who will present the clinical study.

DR. TORIUMI: Good morning. My name is Dean Toriumi. I am an Associate Professor in the Division of

Facial Plastic and Reconstructive Surgery, Department of Otolaryngology-Head and Neck Surgery, University of Illinois College of Medicine at Chicago. My practice encompasses both aesthetic and reconstructive procedures, with emphasis on skin cancer reconstruction, functional and cosmetic nasal surgery, scar revision, and facial cosmetic surgery.

I served as a principal investigator in the clinical study of DermaBond sponsored by Closure Medical Corporation. For this work, my clinic received remuneration for conducting the clinical study. However, I have no financial interest in Closure Medical Corporation or in the product DermaBond. Travel expenses for my participation in today's panel meeting are being paid for by Closure Medical.

I will now review the clinical study of DermaBond. The safety and effectiveness of DermaBond was thoroughly examined in a controlled, randomized, prospective study of over 800 subjects at 10 clinical sites representing a wide spectrum of clinical settings. The overall objectives of this study were to evaluate the safety and effectiveness of DermaBond when used in the approximation of incised or lacerated skin; to compare the performance of DermaBond to currently marketed skin closure

devices, specifically non-absorbable sutures, adhesive strips, or skin staples; and to identify the advantages this device may have over the currently marketed skin closure devices.

These objectives were pursued by studying DermaBond in two indications, which together encompass a wide spectrum of uses encountered in everyday medicine.

Specifically, the indications studied were: closure of surgical incisions or trauma-induced lacerations that could otherwise be closed with 5-0 caliber suture or smaller, where subcuticular sutures would not normally be used; and for the same conditions where subcuticular sutures are used.

The primary effectiveness hypothesis of this study, tested separately for each of the two indications, was that the progress of wound healing at the time of the initial evaluation visit, 5-10 days post-treatment, for DermaBond is equal to or better than that for the currently marketed skin closure devices.

To maximize compliance with the protocol, the time between treatment and the initial evaluation visit was set at 5-10 days, when patients would normally have returned for removal of sutures or staples, and when sloughing of the polymerized DermaBond would generally have

occurred. In the absence of an existing scale applicable to all devices and circumstances encountered in this study, criteria for categorizing progress of wound healing were established to cover the wound conditions likely to be observed at 5-10 days and to standardize the recording of wound healing in five gradations ranging from complete apposition to greater than 50 percent dehiscence.

The secondary effectiveness hypotheses of this study, again tested separately for each of the two indications, were that DermaBond was equal to or better than the currently marketed skin closure devices with respect to the incidence of needing additional or adjunctive securing devices at the time of initial treatment, such as the use of adhesive strips at the time of suturing, which in this context was not considered a failure of the sutures; and the time required for performing the treatment, which was defined to include the time required to close the laceration or incision plus the time subsequently required to remove the closure device, if applicable.

The safety hypotheses of this study, again tested separately for each of the two indications, were that DermaBond was equal to or better than the currently marketed skin closure devices with respect to: the

incidence of wound dehiscence at any time was considered to be a result of a device failure; the incidence of suspected wound infection at 5-10 days; the extent of acute inflammatory reaction at 5-10 days, which was assessed by clinical manifestations of erythema, edema, pain, and sensation of elevated skin temperature; the overall wound cosmesis score at three months using the modified Hollander scale; the incidence of unanticipated adverse device effects at any time.

Three months was selected for making the evaluation of cosmetic outcome since it represents a point at which reasonable judgments can be made of the features comprising the cosmetic appearance of a laceration or incision scar, and there are validated scales for assessing cosmesis at this time point.

Ten clinical sites participated in the study to test the safety and effectiveness hypotheses. The clinical sites were selected to represent a diverse range of clinical specialties and settings reflecting everyday medicine. The spectrum of clinical settings ranged from emergency/urgent care centers to operating rooms and surgi-centers. Specifically, the sites included one general emergency medical center, one pediatric emergency medical center, two urgent care centers, two dermatology

centers, one general surgery center which focused on hernia repair, one OB/GYN center which focused on minimally invasive surgery procedures, one orthopedic surgery center which represented a military medical setting, and one facial plastic surgery center.

While the study was designed and conducted to assess the performance of DermaBond in diverse clinical settings of everyday medicine, it would not have been prudent or practical to study all types of lacerations or incisions in all these settings. Therefore, inclusion and exclusion criteria were employed to define the study subject and wound populations.

The subject inclusion criteria were: that the patient must be at least one year of age and in good health; that the patient has signed the informed consent form; and that the patient agreed to return for follow-up evaluations.

The subject exclusion criteria included: significant multiple trauma (as opposed to merely multiple wounds, which were allowed); peripheral vascular disease; insulin-dependent diabetes mellitus; blood clotting disorder; known personal or family history of keloid formation or hypertrophy; and known allergy to cyanoacrylate or formaldehyde.

To facilitate the conduct of the study and analysis of results, a number of criteria were employed to exclude wounds that would obscure or otherwise hinder assessment. The wound exclusion criteria included: complex or compromised wounds; wounds from an animal or human bite or scratch; those wounds located at a mucocutaneous junction or in mucosa, including the vermillion border of the lip; wounds in scalp covered by natural hair; and wounds normally closed with sutures of U.S.P. size 4-0 caliber or larger.

Consecutive patients at an investigational site who met all the inclusion/exclusion criteria and who had at least one eligible wound were enrolled. Each enrolled subject was randomly assigned to either DermaBond or to the currently marketed control devices. Patients with multiple eligible wounds had all their eligible wounds treated either with DermaBond or control devices. The selection of the type of control device -- that is, suture, adhesive strip, or staple -- was based on the standard of care. Medical judgment determined whether a given wound was treated with subcuticular sutures or without subcuticular sutures.

To provide overall balance in the number of wounds of the two indications treated with DermaBond and

control devices, a stratified randomization scheme was employed to accommodate the diversity of clinical settings.

After the study was completed, the data were analyzed for the with subcuticular sutures and the without subcuticular sutures indications. These were done separately. For patients who had multiple wounds, all eligible wounds were evaluated at the follow-up visits, but at the time of analysis another randomization scheme was employed to select only one wound from the patient for analysis of safety and effectiveness. Dr. Michael Thorn will be speaking next and will describe the statistical analysis and the results of the study. However, before he speaks, it is important that you know a little more about the subjects and their wounds from which these data were obtained.

A total of 818 subjects were enrolled in this prospective, randomized, controlled study, representing a wide spectrum of clinical specialties and settings of everyday medicine. The distribution of subjects in each type of medical setting is shown here.

Of the 818 subjects enrolled, 59 percent were treated without subcuticular sutures, versus 41 percent that were treated with subcuticular sutures.

Upon review of the study, four, or less than

one-half percent of the 818 subjects were determined to be protocol violations warranting removal from the analysis database. Of the remaining 814 subjects treated according to protocol, 95 percent returned for follow-up at 5-10 days post-treatment and 94 percent returned for follow-up at the three-month post-treatment evaluation. The lowest follow-up rate was for control subjects treated without subcuticular sutures, with many of these being from emergency/urgent care centers.

Lastly, I would like to describe the demographics of the study population. The following slides present information on age, race, gender, and anatomical location of wounds.

As one would expect, within each indication, the DermaBond and control groups are closely matched in age. However, subjects with subcuticular sutures tended to be older than subjects without subcuticular sutures, reflecting the age differences between populations experiencing surgeries versus those experiencing trips to the emergency/urgent care centers.

There is nothing particularly noteworthy about the study population with regard to race other than to recognize that the study population reflects a cross-section of the United States population. The same

can be said with regard to gender.

As one would expect, within each indication, the DermaBond and control groups have similar distributions with respect to anatomical location of the wounds. However, subjects with wounds on the torso tended to be treated with subcuticular sutures, reflecting, in part, surgical incisions of the abdomen, and subjects with wounds on the hands tended to be treated without subcuticular sutures, reflecting, in part, lacerations from accidents.

In summary, this study was a prospective, randomized, controlled study of more than 800 subjects with 94 percent follow-up at three months. This study was conducted in a wide spectrum of diverse clinical specialties and settings. Please keep in mind the basic yet comprehensive nature of the clinical study I have described as Dr. Michael Thorn presents to you the analysis methods and the statistical findings.

Thank you for your attention.

DR. THORN: Good morning. My name is Michael Thorn. I am President of Statistical Resources, Inc., and Closure's statistical consultant. I will discuss the statistical methods, analyses, and findings of the DermaBond study.

I would like to begin by presenting the results

of the study, and then briefly describe the analyses used to arrive at our conclusions, that DermaBond is equivalent to standard wound closure devices for both safety and effectiveness based on the statistical analyses. Drs. Hollander and Toriumi will follow to discuss the clinical importance of these findings.

Our primary effectiveness outcome was progress of wound healing at 5-10 days post-treatment. Other effectiveness outcomes included the need for additional securing devices, and the time required for treatment.

The original analysis plan for this study assumed a lower degree of influence of confounding factors on the study outcomes and did not adjust for these potential confounders or statistical interactions. After discussions with the FDA, they suggested regression analysis as an approach which allows for the simultaneous adjustment for multiple confounders and statistical interactions.

The results that I am about to discuss present both the proportions observed in the study together with the P values from the logistic regression analyses. Regression analyses are commonly used to find differences. If differences are not found, it can be for one of two reasons: that there are no differences, or there are

inadequate numbers of patients and therefore lack of power. We designed this clinical trial using a less sensitive measure than logistic regression. We enrolled the targeted number of patients, and therefore finding no statistical difference can be interpreted as equivalence.

Progress of wound healing at 5-10 days, comparing complete apposition to anything less then complete apposition, shows 75 percent for DermaBond versus 89 percent for control in patients without subcuticular sutures, and 84 percent versus 96 percent in patients with subcuticular sutures. These rates were statistically equivalent when analyzed using the regression model, which adjusted for the confounders and statistical interactions.

The other two effectiveness variables were the need for additional securing devices and the time required for treatment.

In patients without subcuticular sutures, 93 percent of DermaBond patients and 95 percent of control patients did not require additional securing devices. This is statistically equivalent. However, in patients with subcuticular sutures, 99 percent of DermaBond patients and 93 percent of control patients did not require additional securing devices. These were not statistically equivalent, but showed superiority for DermaBond.

The time required for treatment also favored DermaBond. In patients without subcuticular sutures, the mean times were 189 seconds for DermaBond and 396 seconds for control. For patients with subcuticular sutures, the mean times were 189 seconds for DermaBond and 274 seconds for control. These differences were statistically significant for both study groups.

For safety, the analysis showed statistical equivalence, or favored DermaBond, for all outcomes. The first outcome, wound dehiscence at any time, showed that there was statistical equivalence between the treatment groups for both study arms.

An additional outcome was the incidence of suspected infection. Again, the results showed statistical equivalence between the treatment groups for both study arms.

Acute inflammation was comprised of four items: erythema, edema, pain, and temperature. For those patients in the no subcuticular treatment group, there was a highly statistically significant difference between the treatment groups in favor of DermaBond. In patients with subcuticular sutures, there was marginal statistical significance with a P value of 0.06, with the trend favoring DermaBond.

Wound cosmesis was evaluated at three months. A modified Hollander cosmesis scale was used for this assessment. The scale employed a 7-point scale with a score of zero reflecting optimal cosmetic outcome. Scores of 1-6 reflected a suboptimal cosmetic outcome. The rates of patients who experienced a less than optimal outcome was statistically equivalent for both study groups -- that is, the with subcuticular group and the no subcuticular group.

Lastly, although there were some adverse events reported in the study, none of the events were unanticipated adverse device effects.

I would now like to briefly discuss the statistical methods and issues regarding logistic regression analyses that were used to analyze these data. I will keep this both basic and brief. However, if the panel has an interest in hearing further details on this methodology, I'd be happy to discuss this further.

It is common in many device trials for the population studied to be very narrowly defined. However, this trial more closely mimics clinical practice in that it includes a wide variety of clinical practice types and patient populations. While this provides clinically relevant data, it requires the use of an analytic method which simultaneously can account and adjust for variability

in multiple confounding factors.

Regression analyses allow for the simultaneous adjustment of multiple variables, both categorical and continuous. This minimizes multiple, sequential hypothesis testing by allowing for the simultaneous testing of multiple hypotheses within a single model.

Logistic regression requires a dichotomous response variable. For linear regression, a continuous variable is necessary.

Therefore, to employ logistic regression, the primary endpoints had to be expressed in a dichotomous form. For example, the original effectiveness endpoint -- progress to wound healing at 5-10 days, which has five categories -- had to be dichotomized into category 1, complete apposition, versus categories 2-5, less than complete apposition.

Likewise, cosmetic outcome at three months on a 7-point scale was dichotomized into zero or optimal versus greater than zero or suboptimal.

Further, all other safety and effectiveness endpoints, except one, can be viewed as dependent variables with a dichotomous outcome. Thus, the need for additional securing devices, dehiscence, suspected infection, and acute inflammation are dependent variables with dichotomous

outcomes -- presence versus absence -- and can be analyzed using logistic regression.

The one dependent variable of the study that is continuous, time for treatment, was analyzed using multiple linear regression analyses.

This slide shows the list of independent variables important for these regression analyses: clinical site or center, which is the same as investigator; type of surgical procedure; type of wound; body location; wound volume -- that is, the length, width, and depth of the wound; subject demographics, which is age, gender, and race; and the use of local anesthetics.

Although an outcome parameter, the need for additional securing devices at the time of initial treatment, was included as an independent variable at the request of FDA.

Sloughing was also of interest, but this could not be utilized because it applied only to one group of subjects, specifically those subjects that were assigned to DermaBond, and therefore there was no comparitor group.

In order to simplify testing, the following logic was used to group some variables. Wounds were classified as either a surgical incision, specifically a skin lesion removal, minimally invasive surgery, or general

or other surgery, or as a type of traumatic laceration, specifically with a smooth or jagged edge. Obviously, it was not possible to have wounds classified as both incision and surgical. Therefore, the type of surgical incision or procedure and the type of laceration were grouped together for testing.

Similarly, clinic variables -- that is, variables that might reflect differences between individual clinics or types of clinics -- were grouped for testing together.

Also, body location of the wounds were grouped together for testing and grouped into four anatomical areas: head and neck, arms, legs, and trunk.

Finally, wound length, width, and depth -- that is, wound volume -- were also grouped together for testing as wound characteristics. The idea was that wounds of smaller volume may have different treatment effects with the various devices than wounds of larger volume.

If we specify an analysis strategy and apply it to all analyses, then a standard procedure is achieved. This provides a systematic presentation and interpretation of the results.

Analyses were performed separately for those subjects with subcuticular sutures and those patients who

did not require subcuticular sutures.

First, we fit a full model -- that is, a logistic regression analysis was performed with all of the variables present.

As pooling across sites was extremely important, we then tested to see if there were differences across sites. Regression analysis in this setting has the advantage of testing clinical site poolability in the presence of adjustments for all the other variables in the model.

If the P value for sites was significant, this indicated that there were differences between the sites, and these terms needed to stay in the mode] to adjust for these differences.

If the P value for sites was not significant, this indicated that sites were poolable, and the site variable was removed from the model. This was then called a reduced model.

Next, the remaining additional grouped variables were tested: the type of surgery or wound, body location, and wound volume.

If any of these other grouped variables were not significant, they were removed from the model, further reducing the model. If they were statistically

significant, then they were potential confounders and remained in the model to adjust for differences between the variable and the outcome.

Then the individual variables were tested. These included: age, race, gender, use of local anesthetics, and need for additional securing devices.

Finally, the endpoint under consideration was tested -- for example, progress to wound healing at 5-10 days, the primary endpoint. However, this test assumed that there were no statistical interactions, only adjustments for variability within levels of the covariates.

At this point, let me say a few words about statistical interactions. Statistical interactions are those differential effects of one variable, such as treatment, across different levels of a second variable, such as gender. A hypothetical example would be if there is a gender-by-treatment interaction, then the treatment effects are different for males than for females.

These interactions between treatment and potential confounders were added into the model and tested simultaneously. If interactions were significant, confounding was present because there are differential effects across the levels of those variables, and treatment

was then reassessed or, in other words, re-tested after adjusting for the presence of these confounding variables.

A non-statistically significant result in treatment differences was then interpreted as equivalence, as this confirms there was no evidence of statistical differences.

I would now like to present the results of the analysis of the primary effectiveness variable, progress of wound healing at 5-10 days, for both study indications, patients with subcuticular sutures and patients without subcuticular sutures.

First, I will review the results in patients who did not have subcuticular sutures. The results indicate that clinical sites were poolable; there were no important differences between clinical sites. There was variability in the outcome variable, progress to wound healing, within the type of surgical procedure or wound, body location, and wound volume. These, then, were confounders.

These confounders and their interactions with treatment were significant. Although the observed rates of complete apposition were less with DermaBond, when using the regression models and adjusting for confounders, these differences in rates were not statistically significant

that is, there is equivalence between the two treatments.

The analysis was repeated for subjects with subcuticular sutures. The results of the primary effectiveness analysis, progress to wound healing, had very similar results. Clinical sites were poolable. The confounders included type of surgical procedure and wound, body location, and wound volume.

The confounders and their interactions with treatment were significant. Once again, we adjusted for these interactions and we found no evidence of differences in treatment, although the P value was marginal.

The exact same process or analysis strategy was followed for each of the other endpoints or outcome variables. Because time required for treatment was a continuous variable, linear regression was used using the same modeling strategy. Other than that, the same procedures were followed for each outcome variable.

Potential confounders and interactions were tested in the same order and the same manner. If any terms or variables were significant, including clinical sites, sites were not poolable and they remained in the model to adjust for these differences.

For the outcome variable "need for additional securing devices," there was no evidence of differences

between treatments in patients without subcuticular sutures, but there was a difference in favor of DermaBond in subjects who had subcuticular sutures.

Mean time required for treatment was not equivalent between the treatment groups. Not unexpectedly, it took less time to close a wound with DermaBond, and this was supported by the linear regression analyses.

For the safety endpoint, cosmetic outcome at three months, the logistic regression analysis demonstrated that the results were equivalent between the DermaBond and the control devices for both study arms.

For dehiscence at any time, the logistic regression analysis demonstrated that the results were equivalent between the DermaBond and the control devices for both study arms.

Although the number of cases of suspected infection appears to be higher in the DermaBond subjects, after adjusting for confounding variables, no differences were observed in the incidence of suspected infections for either those subjects with subcuticular sutures or those subjects without subcuticular sutures. Additionally, these rates of suspected infection for both DermaBond and control subjects were consistent with those commonly reported in the literature.

This slide shows the various components of acute inflammation -- erythema, edema, pain, and temperature -- which are commonly used to identify acute inflammation. In subjects without subcuticular sutures, there were differences in the rates, as seen here, and these lower rates favored DermaBond.

It is also noted that these components -- erythema, edema, pain, and temperature -- are clinical signs that clinicians frequently use in the diagnosis of infection. This further reinforces the results found in the logistic regression analysis for suspected infection.

In patients with subcuticular sutures, the differences were marginally statistically significant. There does seem to be a trend in favor of DermaBond for the erythema and edema outcomes.

We can summarize the findings from the logistic regression as follows. When looking at the outcome measures of progress to wound healing at 5-10 days, as well as the other effectiveness measures, the results showed that treatment with DermaBond and control were statistically equivalent. Wound dehiscence at any time was statistically equivalent. Suspected infection was statistically equivalent. Acute inflammation was superior in the no subcuticular sutures group, and marginally

statistically equivalent in the with subcuticular sutures group. The P value was 0.06. Wound cosmesis at three months was statistically equivalent. There were no unanticipated adverse device effects for any patient in either treatment group in this trial.

We can conclude that, after adjusting for confounding variables in this clinical trial across a wide variety of clinical specialties and settings, there was no evidence of treatment differences, or if there were differences, these differences favored DermaBond. This is statistical equivalence.

Thank you for your attention. At this time, I would like to turn the presentation over to Dr. Judd Hollander who, together with Dr. Toriumi, will discuss the clinical significance of these results.

DR. HOLLANDER: Good morning. I'm Judd Hollander. I'm the clinical research director and associate professor of the Department of Emergency Medicine at the University of Pennsylvania. While at my former institution, the State University of New York at Stony Brook, I was a co-investigator for the DermaBond study. For the study, I did not receive any individual remuneration. However, my institution received funding. But in the interest of full disclosure, I have to tell you

that after completion of the trial, assuming my relationship with Closure had terminated, I purchased a small amount of stock in the company. When Closure contacted me and asked me whether I would be willing to present before the FDA, I sold those shares. I do not now have any financial interest in the company. Closure will reimburse me for my travel expenses for this presentation.

My background in clinical wound management is based upon the development of the wound registry, which is a large database that we've collected over the last five years, leading to multiple investigations in wound management, particularly with an emphasis on cosmetic outcome. As a result of this expertise, I became involved with Closure.

Because many of the particular variables and outcomes in this trial are similar to those we used in our validated data collection instrument, I would like to spend a moment describing the wound registry development and validation. In addition, I will then place the use of DermaBond in context with my experience based on over 5,000 lacerations in this registry.

The wound registry development began with a formal survey of practitioners from which we developed an initial data instrument. After assessing inter rater

reliability, we piloted a phase of data collection, refined the data instrument, and then did some final validation measures, particularly for the cosmetic outcomes.

The data that we routinely collect is age, race, gender, past medical history, time from injury to evaluation. We collect lots of data regarding wound description, such as the etiology of the wound, the anatomic location of the wound, size of the wound, shape, alignment with skin, tension lines, whether the margin edge is smooth or jagged, depth of the wound, and any visible contamination or foreign bodies.

With regard to wound preparation, we record the type of block, the anesthetic agents used, methods of cleansing, particularly the instruments used, the fluids used, the use of debridement, and any creation of flaps to close wounds.

With regard to wound closure, we look at layers of closure, type and size of suture material, the type of suture material used, and the type of stitch, as well as the number of sutures placed.

Postoperative wound care is divided into that which occurs in the emergency department and that which occurs after discharge. In the ED, we record the use of topical antibiotics, the type of dressing, after discharge

what their prescribed topical antibiotic is, systemic antibiotics, and any plans for follow-up. In addition, we record the level of training of the practitioner.

At the time of follow-up, we record the presence or absence of erythema, warmth, tenderness, and drainage, and then the presence or absence of infection, which can be classified as follows, into four different categories.

Of particular relevance in this trial is the cosmetic appearance scale that we use, where each wound is classified on one of six parameters. They are step-off of borders, contour irregularities, margin separation, edge inversion, excessive distortion, and overall appearance. Overall appearance is considered to be an adjustment factor for when something is wrong with the wound that is not taken into account by the first five categories. They're assigned zero or one point each for each of these items, and then the total cosmetic score is tallied. Once it's graded from zero to six, it's split categorically into optimal and suboptimal.

Looking at the individual items in the registry, we've demonstrated that most of them have almost perfect concordance with inter-rater reliability and kappa values greater than 0.8, or in the 0.6 to 0.79 range.

Depth has a fair concordance with a kappa that was in the 0.4 to 0.59 range.

Of more relevance is the overall cosmetic outcome score, divided into optimal and not optimal, where short-term and long-term kappa values are both greater than 0.6, and concordance on infection was very high. It was 1.

With respect to the series of validation studies that we've done with this scale, short-term validation was assessed at the time of suture removal, which corresponds very nicely to the 5-10 day follow-up used in this trial. Long-term validation was conducted up to nine months later, and then to assess external validity, we compared the physician's rating of this cosmetic scale to patient satisfaction at three months.

The modifications used in this trial really do not represent significant modifications. We simply attached more detailed definitions to each of the individual items in the scale. This would only be expected to further enhance the reliability of a scale that was already shown to be reliable.

As I'm sure you're aware, early wound healing attains less than 10 percent of its original tensile strength within the 5- to 10-day period of edge apposition was assessed in this trial. As a result, the short term

cosmetic outcome at that time period might not be expected to bear a very strong relationship to the long-term cosmetic outcome when wound remodeling is complete, nine to twelve months later.

Based upon my clinical experience and the published literature where this issue has been addressed, it's been found that this is true. For example, lacerations that may appear excellent in the very short term may be suboptimal after wound remodeling is complete. More surprisingly, lacerations that don't look great in the short term may appear quite fine many months later when wound remodeling is complete.

In our studies of this issue, we did not specifically assess edge apposition. However, margin separation, one of the items in our scale, very closely corresponds to edge apposition. Because those categories are analogous, I would expect that the short-term edge apposition may not correlate very well with the three-month cosmetic outcome, which of course is much more important than the short-term cosmetic outcome.

This is a slide of a patient who was treated with DermaBond during the study at the time of suture removal. It's important to look at the edge apposition scale that was used in this study in concert with this

slide. The scale was interpreted as complete apposition, less than 50 percent epidermal separation, or more than 50 percent epidermal separation. As you can see, with the adhesive overlying the scar it's very difficult to determine this endpoint, making this a relatively soft characteristic. I think if all of you look at this, it's kind of hard to tell whether that's adhesive there or there's a little separation. In trying to use this as an endpoint, we're left with something that's relatively subjective, which wasn't anticipated when the trial was designed.

For this reason, I had suggested to Closure that it may be more appropriate to analyze the data by combining the complete apposition and the less than 50 percent separation groups, since most of the patients where you couldn't see if there was complete apposition would be anticipated to have a very small degree of separation.

When this was done, when the complete apposition and less than 50 percent separation groups were combined, DermaBond and control did not differ. At the suggestion of the FDA, a logistic regression analysis was done to control for confounding variables. Once again, DermaBond and control were not different. Although the interaction terms employed in the logistic regression model

may be confusing, it doesn't make a lot of clinical sense to disregard all the clinical variables that we know are incredibly important in determining wound outcome. As a result, I think the FDA's suggesting using logistic regression to look at this parameter is probably the right way to go, because it is critically important to control for these wound characteristics that we know influence cosmetic outcome.

Regardless of the analysis methods, the clinical meaning of this progress of wound healing scale is not nearly as important as the long-term outcome, where the DermaBond and control groups were almost identical.

Our experience at Stony Brook, which is an academic emergency department, level 1 trauma center, tertiary referral hospital, serving a population base of over a million people, with an annual ED census of 47,000 patients. Investigators at our site were eight full-time emergency physicians who had repaired over 1,000 lacerations in the five years preceding this study. To train for this study, they viewed a brief 20-minute videotape and practiced applying DermaBond to frankfurters two to three times before patient applications. None had had any prior octyl cyanoacrylate experience.

We enrolled 124 patients, and based on the

experience at our institution, we found DermaBond to be easy to use, with a very rapid learning curve, comparable short- and long-term cosmetic outcomes to sutures, and a low infection rate that was about the same that we observed in our 5,500 patients in the wound registry. The one infection at our institution was clearly the result of poor local wound closing. It was a child who had gotten hit in the head with a baseball bat, fell down in the garden, and came into the ED with a laceration over the eye. The clinician decided not to use local anesthesia, actually probably never cleansed the wound at all, applied the DermaBond and sent the child home. The child returned two days later with an infection and was found to have a twig from a branch that was in the garden inside of the wound.

It was the opinion of the investigators that the trial's inclusion/exclusion criteria are entirely appropriate indications for the use of DermaBond. Based on those criteria, my extensive wound registry experience, we can estimate that about 30 to 40 percent of ED lacerations would probably be eligible for use of DermaBond.

I think the use of DermaBond, as I mentioned, is probably appropriate for closure of traumatic lacerations repaired in the ED. It's clearly comparable cosmetic outcome to sutures. The infection rate is

comparable with large cohorts of patients in the emergency department.

Patients have found the use of DermaBond to have much less pain associated. The rapid application makes it certainly preferable to sutures. In addition, because suture removal is not needed, the use of DermaBond should reduce the cost and improve the convenience of traumatic laceration repair.

In conclusion, I think the addition of tissue adhesives to our armamentarium of wound management tools should provide a rapid, painless alternative to sutures for approximately one-third of patients with traumatic lacerations.

I'd now like to turn the presentation back to Dr. Toriumi, who can discuss his clinical experience.

DR. TORIUMI: Thank you, Judd.

At the University of Illinois, we were fortunate to enroll 111 patients in our study. We had 54 test patients, 32 of which underwent subcuticular closure with DermaBond, and 22 that had closure with DermaBond alone. There were 57 control patients, 34 of which underwent subcuticular suture closure followed by skin closure of the epidermis. Twenty-three patients underwent suture skin closure alone.

Procedures were performed primarily on the face. Most of the procedures involved excision of skin lesions and tumors, benign tumors, scar revision, and closure of post-traumatic wounds. I performed all of the procedures in the follow-up, and our study was 110 of 111 patients showed up for the 90-day follow-up visit.

In our study the results showed no evidence of wound dehiscence, there were no wound infections, and overall we found that the cosmesis of DermaBond was better than that of controls, with less inflammation and erythema, no widened scars or suture tracks, and excellent scar camouflage.

Interesting to note is the time of application of each of these respective skin closure devices. In these particular situations, the time measured here only involved the time of the application of the skin closure device and not removal of the sutures at postop visit. For sutures, we see that the mean was 3 minutes and 47 seconds, whereas for DermaBond, the mean was 45 seconds. However, when we combine the treatment time of both groups, we come up with a total treatment time of 225.1 minutes, and when you break it down between sutures and DermaBond, 194.55 minutes, or 86.4 percent of the total time required was devoted to suture closure, whereas 30.55 minutes or only 13.6 percent

was devoted to the application of DermaBond.

The wound appearance at 5-10 days with the early visit revealed that the incisions were barely detectable, with only a fine line noted. The incisions had less erythema than the control group, and there were really no lacerated skin edges or eschar noted in any of the test wounds.

Here's an example of a patient who presents 21 days after the surgical procedure, and we note a vertical scar here which is fairly well camouflaged. This is a wound that was treated with DermaBond. In the same patient, an adjacent wound which was a stellate scar, therefore it was excluded from the study, but just for comparison purposes I want to show you it was closed with vertical mattress sutures, and you can see the difference with the erythema, the edema, and the suture marks noted. This was pretty characteristic of what we saw with comparison of the two wounds.

The 90-day results showed excellent scar camouflage, no widening of the scars, no suture tracks, and no incisional pain or prolonged erythema.

Now I'd like to take you through two patients who go through the preoperative situation, as well as through the operative procedure. This patient presents

with a benign lesion in the left temporal region. She opted not to undergo shave excision and wanted the lesion completely excised. Therefore, we performed a fusiform excision just anterior to the temporal hairline. We see the defect here. The skin edges were approximated with a subcuticular closure, and then with the skin edges apposed, the DermaBond was then applied to complete the epidermal closure.

This is the patient at the three-month follow-up visit, and we see relatively good camouflage of the scar in the left temporal region.

This patient presented with a mass in the left forehead presumed to be a benign lipoma. This was removed through a horizontal incision. This is the lipoma, which upon pathologic analysis was verified as a benign lipoma. We have approximation of the epidermal skin edges with deep subcuticular sutures, and then preparation of skin epidermal closure with the application of multiple thin layers of the DermaBond in three or four strokes to complete the closure process.

The patient then presented back to us at seven days postop, showing sloughing or peeling of the edges of the DermaBond, with relatively good healing of the underlying scar. The 90-day visit reveals a relatively

good camouflage of the horizontal scar in the forehead region.

When comparing DermaBond to skin sutures, we found it had superior cosmetic result to sutures, it was very desirable to patients, and we found excellent long-term results.

Some technical points that we found to be important with the use of DermaBond was that it's important to insure good hemostasis, careful preparation of the wound and handling of the tissues. We wanted to use everting subcuticular sutures whenever possible to maximize the cosmetic result, and we tried to apply the DermaBond on a horizontal surface to prevent it from running away from the incision site itself. We also liked to use multiple thin layers of the DermaBond to decrease the heat that's transmitted.

Now, in this case, when we looked at the subcuticular sutures used with DermaBond, it was primarily when skin edge eversion was difficult to achieve. Patients with thick skin of the forehead, cheek, and chin were situations where we preferred to use the subcuticular closure. Also, in wounds where we wanted to decrease the tension at the epidermal skin edge closure.

This is a similar type of illustration that was

provided to all the investigational sites just to verify what we're talking about with respect to verbiage when we talk about a subcuticular suture closure.

This color illustration just illustrates favorable bevelling of the skin edges with the application of a subcuticular closure. Good approximation of the epidermal skin edge with then application of the DermaBond to complete the closure of the epidermis.

The learning curve was interesting in that it was relatively short if a physician adhered to the principles of soft tissue technique. Previous surgical experience was definitely helpful, and use of the material in a practice setting allowed the surgeon to aid in managing the viscosity and setting time, which took some degree of experience with the applier.

The time savings were really important. Use of DermaBond avoided the need for application of skin sutures. There was significant time saved in eliminating the need for suture removal, and there was less postoperative follow-up because of the rapid resolution of inflammation.

To conclude, when using DermaBond in facial plastic surgery, it was particularly helpful in sebaceous skin with a high incidence of suture tracks, such as the nose, forehead, and chin. It was also very helpful in

thin-skinned areas where we really do not need excessive skin edge eversion, such as the eyelid and the neck skin. It was also very helpful when suture removal was problematic, particularly in the pediatric population or in patients who travel out of town for treatment.

Thank you for your time. Now I'd like to ask Joe Barefoot to return to the podium.

MR. BAREFOOT: This study of 818 patients with 94 percent follow-up, to our knowledge, is the largest, most comprehensive, and most rigorous study of a laceration or incision wound closure device. The study was designed and was executed to meet the FDA criteria for valid scientific evidence. Specifically, the study was a controlled, randomized study. Stringent statistical hypotheses and analyses plans were formulated to compare DermaBond to currently marketed control devices on clinically significant performance parameters. Sufficient numbers of subjects were enrolled to provide adequate data bases for statistical analyses and clinical judgements.

Care was taken to assure that the study included clinical investigators, subjects, and types of wounds to adequately address every facet of the cross-section of the anticipated use settings, ranging from hospital emergency departments and urgent care centers to

settings of general and plastic surgeries. Further, care was taken to achieve adequate representation of settings, patients, and wound types, while still preserving the integrity of randomization.

Fundamentally, successful medical management of skin wounds from traumatic lacerations and surgical incisions seeks promotion of wound healing and avoidance of dehiscence, infection, acute inflammation, pain, and adverse cosmetic outcome. These important clinical outcomes matched our study endpoints.

To this end, the logistic regression analyses and other statistical methods applied to the clinical data from this study, which included the diverse clinical settings of everyday medicine, demonstrate that for both wounds closed without subcuticular sutures and wounds closed with subcuticular sutures, the results for progress of wound healing at 5-10 days and cosmetic outcome at three months were equivalent for the DermaBond and control groups.

The other conclusions from this study are: dehiscence rates were equivalent for the DermaBond and control groups; overall rates of suspected infection were equivalent for the DermaBond and control groups and were consistent with commonly recognized rates of infection for

sutured wounds.

Incidence rates of the clinical signs that comprise the study definition of acute inflammation, which were erythema, edema, pain, and temperature, demonstrate that there was less acute inflammation in the DermaBond group than in the control group -- that is, the results favored DermaBond when no subcuticular sutures were used. When subcuticular sutures were used, acute inflammation was equivalent for the DermaBond and control groups.

The rates for needing additional or adjunctive securing devices at the time of initial treatment were equivalent for the DermaBond and control groups when no subcuticular sutures were used. However, when subcuticular sutures were used, the rate for needing additional securing devices was less in the DermaBond group than in the control group -- that is, the results favored DermaBond.

The time required to perform treatment -- that is, the time to place and remove wound closure devices -- favored DermaBond.

Thus, the study provides valid scientific evidence of the safety and effectiveness of DermaBond as a topical skin closure adhesive for traumatic lacerations or surgical incisions under conditions of use both with and without subcuticular sutures. Hence, there is necessary

and sufficient evidence to conclude that FDA should approve DermaBond with the indication for topical application to hold closed approximated wound edges of trauma-induced lacerations or surgical incisions, including punctures from minimally invasive surgery, that otherwise could be closed with sutures of U.S.P. size 5-0 caliber or smaller, staples, or adhesive strips.

Moreover, the results of this study of 818 subjects are entirely consistent with those of another prospective, controlled, randomized study of DermaBond recently conducted in Canada in 130 subjects, which was published in JAMA last year by its investigators.

As important practical considerations, DermaBond provides the significant advantage of avoiding the pain and anxiety associated with suturing, and there is no need for patients to return to the clinic for removal of DermaBond, as would be the case with sutures or staples. The use of local anesthetics to avoid pain during treatment of traumatic lacerations was reduced in the DermaBond group.

The resulting economies of resources, time, and travel are of potential benefit to both the health care provider and the patient.

This concludes our formal presentation. During

the question and answer portion of the program, we want to remind you that Dr. Bruns is a specialist in pediatric emergency medicine and would be happy to share his experience with you. Also, Dr. Toriumi has collected one-year follow-up data on his patients. This data was collected by Dr. Toriumi under his own protocol and was not part of the Closure data. After your deliberations, he would be happy to share the data with you if you desire.

Thank you for your attention. We would be pleased to answer any of your questions at this time.

DR. MORROW: Thank you.

We'll now have questions from the panel to the sponsor.

Dr. Chang?

DR. CHANG: I'd like to know your rationale for selecting three months as the long-term follow-up, when average time for maturation was stated as nine months.

MR. BAREFOOT: I'd like to call one of our clinical investigators to respond to that question.

DR. HOLLANDER: Hi. Judd Hollander again.

Part of it obviously had to do with study duration and time, but there is data out there, both pathological and clinical, that the three-month follow-up or three month cosmetic outcome correlates very well with

the nine-month or one-year cosmetic outcome. So that seemed to be a good surrogate where, although remodelling is not complete, if the wound looks good, it continues to look good, and if the wound looks bad, it continues to look bad.

DR. MORROW: Other questions? Dr. Boykin.

DR. BOYKIN: I'd like to ask Dr. Toriumi some questions. As a plastic surgeon, I'd like to discuss with you the cases that you personally handled. If you had not used DermaBond on some of these facial cosmetic cases, what would you have used as a skin closure?

DR. TORIUMI: Vertical sutures, probably 6-0 nylon.

DR. BOYKIN: Would you ever have considered using steristrips with mastisol or --

DR. TORIUMI: No, because I really wanted to get some skin edge eversion, which you can get with the DermaBond. DermaBond has a biomechanical stability and rigidity to it that allows you to actually elevate that epidermal edge, which you really can't get with steristrips. That is, in my mind, a significant advantage over the steristrip.

DR. BOYKIN: Did you have any problems adjusting the edges of the skin to apply the DermaBond?

DR. TORIUMI: After performing just a handful of cases, it's really amazing how you can get control of the skin edge with or without the use of forceps to allow the epidermal edges to come together very nicely, and that allows you to apply a thin layer of the DermaBond and complete your closure.

DR. BOYKIN: The reason I was asking the specific question is that usually in facial cosmetic work, if we do a fairly good subcuticular suture, the rest is a given. You should go fairly well with steristrips, mastisol, even some other topical adhesives that we have available right now.

DR. TORIUMI: Well, particularly with my experience with the face, I really like to try to maximize the skin edge eversion as much as possible because, as you all know, as time goes by, that wound will stretch and that everted edge will flatten out. I think if that wound can stay everted at two to three weeks, I think we're in real good shape. That's one of the main reasons why I think the mechanical strength itself of the DermaBond allows you to elevate that epidermal skin edge -- not as much as a suture, mind you, but definitely more than a steristrip.

DR. BOYKIN: Let me give you another for instance. You're doing a closure and you're going to use

your 6-0 nylon mattress suture. You're moving along and all of a sudden you realize that, for whatever reason, there's incorrect alignment of the skin edges. You normally remove the sutures, go back, and start over again.

Now, what happens when you're applying the DermaBond and as it's reaching its tensile saturation point, you realize that it needs to be reapplied? Can you strip it off? And what happens when you strip it off the skin? What kind of damage?

DR. TORIUMI: You can use vaseline or petrolatum, things of that sort. In some cases you can try acetone. But in my experience you just apply a little vaseline around the incision, let it sit for a couple of minutes, and that will elevate off very easily.

DR. BOYKIN: So it comes complete with all --

DR. TORIUMI: Yes.

DR. BOYKIN: Have you had a chance to study the patients that you've done this in?

DR. TORIUMI: Fortunately, we've only had one patient that we had to elevate the DermaBond off in that situation that you're just explaining, and it came off very nicely and allowed us to then reapply with really no increase, at least as I comprehend it, no increase in inflammation related to the elevation of the DermaBond, and

then reapplication.

DR. BOYKIN: That's really a group that I'd like to see discussed. How many others within the study group had that situation in which the DermaBond had to be removed and reapplied during treatment?

DR. TORIUMI: The one case where it was removed was a situation where, when I looked at it -- you can see through the DermaBond. That's another really nice issue there. You can look very carefully and very closely under loop magnification and you can see the epidermal edge. If it's just not where you'd like it, you can remove it and reapply it.

DR. BOYKIN: That's germane to practice that we see on a day-to-day basis. Sometimes you're making adjustments. Sometimes it's very important to be able to come back and do this without causing further harm to the skin edge.

DR. TORIUMI: Absolutely.

DR. BOYKIN: We'll discuss this later.

DR. MORROW: Could you clarify something for me on your proposed label? As I read that slide, it says you're proposing this for use in wounds that would be closed with a 5-0 or smaller suture, or wounds that would be closed with staples or steristrips. Is that correct?

MR. BAREFOOT: That's right.

DR. MORROW: Those are not necessarily overlapping subsets of patients, in that there are many physicians who close lots of wounds with staples that they would use a larger suture size on. So does that mean you are in actuality proposing this for use in any laceration?

MR. BAREFOOT: No. Actually, I think the important point is the 5-0 suture reference.

DR. MORROW: Thank you.

DR. DUNCAN: Where did the 5-0 suture reference come from? What kind of studies did you use to dictate that 5-0 is the appropriate suture that you would compare it to, versus 4-0 or 3-0?

MR. BAREFOOT: That was a combination of medical advisors leading us to a way of describing how to use the glue or the limitations, if you will, along with the biomechanical tests that I described in the earlier part of the presentation, where we were going to the rat model where we were using comparisons against suture, the 5-0/6-0 suture, and we did throw in the Histoacryl product as a point of reference as it is used outside the United States, and the glue, and applied a vacuum to those wounds so that you're taking the failure in those tests to indicate that that was a good reference point.

DR. MORROW: Other questions? Yes, Dr. Whalen.

DR. WHALEN: The original five-stage wound assessment for the short term, it was clearly pointed out, was brought to a dichotomous variable for apparent reasons. However, in the one example that I saw of a short-term wound that was placed on a slide, the confusion, at least that was pointed out and that I could readily see, was whether underneath that film there was any apposition at all.

So my question is how reliable, then, are the observations in the short term, even in a dichotomous variable situation, nevermind a five-level situation, when the film obscures whether there is apposition or not?

MR. BAREFOOT: I'd like to ask Dr. Hollander to come to the microphone to answer that.

DR. HOLLANDER: I think that's an excellent point, and that's the point I was trying to make. Unfortunately, when you set up these trials, it makes sense to look at short-term outcome as one of your primary endpoints, and since no one had experience with this product of the clinical investigators, none of us were, frankly, smart enough to realize there may be some problems interpreting it at that time.

So I think the real answer is that it's

difficult to tell. Not all cases are impossible to tell. I mean, in a reasonable number of cases it's very clear if they're apposed or not apposed. I think where the difficulty is is when maybe they're apposed and maybe they're not, and how much apposition is there.

I think the real answer to the question is what patients want, which is a scar that looks nice in the long term. So I think it's really not that important if you can tell that very well at a week. You definitely need to tell it when you're setting the wound, and then the DermaBond is very clear. So you can either wipe it off or lift it off and re-do the wound. I think that's critical.

I think the other critical point is down the road, and I think we know down the road that the two groups are comparable. I think what we really don't know is exactly how it measures up at the time of suture removal. But depending on the analysis you do, it all seems to fall out about the same.

DR. WHALEN: You also, I think, had some very cogent discussion about the variations of short-term appearance versus long-term appearance. As a pediatric surgeon, I pay my rent by doing pediatric hernias with the exact same incision and the exact same closure week after week after week, to the tune of hundreds of cases per year,

and I'm constantly amazed at the occasional patient I see in long-term follow-up, which amounts to a large number, in the variation in wound appearance from patient to patient with the exact same technique, by the exact same surgeon, with the exact same materials.

The conclusion in my mind was simple, then: With that sort of standardization, there's a difference in biochemical parameters in wound healing in the individual patient well beyond anything that we apply. Would you agree with that?

DR. HOLLANDER: Yes, I would agree, and that's why I'm glad to have a trial that was really relatively diverse and took patients from all clinical settings, because at least it kind of mimics what's out there and what we deal with. I think that's the only good way to look at it. I think if you define your population too narrowly, you won't know what other patients may have, some of the variability that you mentioned.

DR. MORROW: Dr. Howell?

DR. HOWELL: I just had a quick question for Dr. Hollander. My understanding of the way the study was designed is that wound cleansing and wound preparation was not standardized across all of the different clinical sites. Is that true?

DR. HOLLANDER: That's correct.

DR. HOWELL: Do you see that as a strength or a weakness? Obviously, you've looked at various clinical settings, different kinds of patients, different kinds of practitioners. By the same token, that one independent variable wasn't controlled.

DR. HOLLANDER: Right. Well, part of it is an artifact of the diverse settings. I mean, for example, you're not going to clean your wound after you incise it. So the surgical cases are clearly different than the traumatic lacerations. There were two emergency departments and two urgent care centers, and there definitely appears to be some diversity. The type of solution used for cleansing was recorded. The volume was not, and whether it was actually irrigated or scrubbed is difficult to discern.

I've tried looking through the data to look at local anesthesia as a surrogate, because I think I would make the assumption that if a patient with a traumatic laceration did not receive local anesthesia, they probably didn't get one of the more vigorous cleansing methods, although that's not true in all cases. And that's why I think you need something like logistic regression to throw in the use of local anesthesia really as a surrogate for

wound cleansing to see whether the outcomes are different.

To answer whether it's a strength or a weakness, it's a little of both. You would clearly know what the answer is in a patient population with a specific type of cleansing had that been used. On the other hand, I think what we do in day-to-day practice is very diverse. So we sort of encompass the whole spectrum of patients that are out there.

DR. HOWELL: It just seemed to me that the logistic regression the way it was done wouldn't really account for that independent variable, because one physician could do it differently from time to time.

DR. HOLLANDER: Most of the sites had a very limited number of physicians who were participating. We had the broadest site. We had eight investigators. I think the second-largest number of investigators was four. So, for the most part, that variability disappears. For example, at Dean's site, he was the only one doing it. At many of the sites it was a single investigator, so it should be relatively standardized. In the emergency department settings, you're right, it's a little more diverse.

DR. HOWELL: The other question I had goes to indications in terms of the patients who were included and

excluded in the study and the wounds that were included and excluded. The way I read it, it seemed that the wounds that were incised in immune-competent hosts, not on significant hair-bearing surfaces, pretty straightforward wounds, not the victims of significant blunt force trauma, those kinds of things -- that seems to be a pretty narrow subpopulation of folks who come in with traumatic wounds.

By the same token, I heard you talk about a baseball bat to the head. Was there some bleed-over in terms of who was included and excluded in the study?

DR. HOLLANDER: Well, basically the inclusion I think, at least as it went up on the slide -- and I actually don't remember the exact wording on the study protocol -- was significant blunt trauma. So I think there was some variability. I did not take care of the child with the baseball bat to the head, so I don't know the specifics of that injury, but I know that is how he got hit. I would only presume that it wasn't when someone was swinging. I know it happened in a garden, so it may not have been a significant blow. But I can't comment on that.

Significant crush injuries were excluded by protocol.

DR. MORROW: Dr. Biros?

DR. BIROS: This is to help me put this in the

context of the emergency department. I want to ask you a question about your wound registry. You said you had 5,000 wounds. Are these traumatic from emergency department centers?

DR. HOLLANDER: Right. It's 5,500 almost consecutive patients who presented to the ED.

DR. BIROS: And is that the basis of your 30 to 40 percent rate that you said would qualify for this?

DR. HOLLANDER: Right. At some point, months and months and months ago, I had taken the inclusion/exclusion criteria and played them through the registry data, and it came out that it was in that range.

DR. BIROS: And in this registry, what is the rate of wound infection?

DR. HOLLANDER: It's in the 3 to 4 range. I think the last time I actually looked it was 3.6 or 3.4.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: I wanted to visit the issue of equivalence. I'm blocking on the biostatistician's name. I'll direct the question to you, and if you're not the appropriate responder, we can change that.

If I remember correctly, your null hypothesis is that you were looking at differences between control and DermaBond. Is that correct?

DR. THORN: We were looking for equivalence.

DR. JANOSKY: Your null hypothesis? What was the statement of your null hypothesis? I have a copy of an overhead here, a thing from the FDA, but if you've got the wording that you were using --

DR. THORN: The original hypothesis was that DermaBond -- well, the null hypothesis was that DermaBond is worse, and that the alternative would be that DermaBond would be equal or better.

DR. JANOSKY: So the trial was looking for equivalence or difference?

DR. THORN: The trial was looking for equivalence.

DR. JANOSKY: So all the hypotheses that you're reporting in terms of differences -- namely, the time -- we would not consider those as differences. Your hypothesis is investigating equivalence, so we either say things are equivalent or not equivalent, never saying that they're different, that hypothesis testing does not lead us down the road of difference. So we cannot come to that conclusion, that the times are different. Is that correct?

DR. THORN: The way that the hypotheses were set up is that we were looking for either statistical equivalence, which would in the regression analysis

framework be non-significant result -- does that answer your question?

DR. JANOSKY: It leads to my conclusion, which is that you can't state a difference if you're looking for equivalence. These two hypothesis testing techniques are very different.

DR. THORN: Well, if you find no statistically significant difference in the regression analysis situation, that could be for two reasons. One of the reasons could be that there truly is no difference, and the other reason would be that you just don't have enough patients, you don't have enough power. We designed the trial assuming an equivalence test, the standard type of bioequivalence test, which is much less sensitive. It does not adjust for all the confounders, and we enrolled that number of patients. Logistic regression is much more sensitive. It allows for all the adjustments of the covariates.

So we believe that we're in a situation where we have no difference because we would have adequate power to find a difference if it existed.

DR. JANOSKY: But hypothesis testing for equivalence is very different than hypothesis testing for difference. So our sample size estimations for equivalence

are different. Our analyses are different if we're looking for equivalence or if we're looking for differences.

When you ran your logistic regression, you were looking for differences? Your inclusion and exclusion criteria for variables in that model were based on statistical significance as you presented it to us today.

DR. THORN: Right. That's correct, and we found no statistical difference. They were not statistically significant.

DR. JANOSKY: But that doesn't necessarily mean that they're equivalent. That's a very different concept than not being different. So if we look at that major hypothesis, which is wound healing for the group of no sutures or with sutures, we're testing equivalence or we're testing differences. Which one?

DR. THORN: That's correct. I mean, I think that there are a couple of issues. One is that the logistic regression allowed us to adjust for the different covariates, to adjust for those differences. The other issue was the suggestion that Dr. Hollander had. Because of the difficulty in the accuracy of what the progress of wound healing was at five to ten days, to actually use the standard original hypothesis -- when you do that, then they do come out equivalent.

DR. JANOSKY: They come out that they're not different, which is not equivalence. Those are two different concepts.

DR. THORN: If you apply the original hypothesis test to the progress to wound healing at five to ten days, you combine categories 1 and 2, then they do come out as being statistically significant -- i.e., equivalent -- using the original hypothesis.

DR. MORROW: Perhaps after we hear the FDA's statistical presentation, we can revisit this, if necessary.

Dr. Burns.

DR. BURNS: I had a question that I think relates to the potential safety of the product, although it didn't initially come up in the sponsor's presentation.

There has been, I think, at least one report in the literature that if there's any residual cyanoacrylate monomer in a polymerized product, that that potentially can degrade to formaldehyde or result in formaldehyde development. Is that something that you test for, or have you looked at that in your product to see whether that's something that potentially could develop?

I also noticed that in the contraindication, you had something for patients who are potentially

sensitive to formaldehyde.

DR. CLARK: My name is Jeff Clark and I'm the Vice President of Research and Development for Closure.

One of the things that we had done was to form a systematic extraction of the product under circumstances that are defined under the U.S.P., using specified surface area preformed polymer films. We would use saline to extract these materials at 50 degrees Centigrade, and we did this for 15 consecutive 24-hour periods and analyzed the extract. In the extract we did find parts per million concentrations of formaldehyde, but no residual monomer was detected there.

DR. BURNS: And from your safety testing, you're satisfied that that level of formaldehyde is --

DR. CLARK: Yes. The extraction conditions that we used in that analysis were identical to the extraction conditions that were used for the safety testing.

DR. BURNS: Just one other question, and that is that it must be hard to sterilize a product like this. I'm just wondering how do you sterilize it, if you can talk about that, and what type of sterility insurance level you would have.

MR. BAREFOOT: Well, as a matter of fact, you

may be aware that the European community requires having it sterilized to be put on the unit label or -- excuse me -- the box label. You're right, there are some challenges to sterilizing cyanoacrylates. This product, the ampule containing the monomer is heat-sterilized, followed by the assembled product being ETO-sterilized.

DR. BURNS: Thank you.

DR. MORROW: Dr. Howell?

DR. HOWELL: Just one other question or two for one of the clinical investigators.

DR. MORROW: Why don't you ask the question first and then they'll pick.

DR. HOWELL: I'm sorry. The question has to do with infection rates. Basically, what I want to know is that it looked like there was a three- to four-fold increase in the infection rate, although not significant statistically, for the DermaBond product versus control. I didn't really understand that. It looked like basically there was a cohort of wounds or subjects with wounds that are fairly simple and straightforward in immune-competent hosts with not a lot of devitalized tissue, not a lot of horrible-looking wounds.

I don't understand why there would be a trend again, not a significant trend, but a trend towards

increased infection in those wounds, given the fact that if this were to play out as a three- to four-fold increase in more complex wounds that were more prone to infection, the 10 to 15 percent rate, it might be significant to the patient and statistically significant. I didn't understand why that would occur with this product, given the fact that there should be less suture material going into the wounds and there really should be less set-up for infection.

MR. BAREFOOT: Let me ask Dr. Hollander to address that question for us, please.

DR. HOLLANDER: I actually was perplexed by the same thing, and we spent a lot of time looking at this. I think the first thing you alluded to is clear, there's no statistical difference, but the numbers kind of jump out at you and warrant an explanation.

I went back and looked at all the preclinical data in the animal studies where the infection rate was exceedingly low. Most of those were with the butyl compounds, but the octyl cyanoacrylates were the same way. There really wasn't a significant infection rate.

Quinn actually has a nice study they published in Surgery at some point last year that actually found that it's actually antimicrobial, the octyl cyanoacrylate as well. In fact, 25 percent of wounds that had I forget

what bug -- maybe it was staph dumped into it actually were sterile when they were examined with the glue but not with sutures, and there's been similar data. I know you're familiar with that.

With that background, it didn't make a lot of sense, so I actually went and looked at the individual cases. The real answer is that the definition was suspected infection and not infection, and people were pretty liberal with what they would consider suspected infection. So here the indication written for Darvocet somehow got called an infection. It was pain. There was no treatment with antibiotics at any time and no complications.

Here the patient received one gram of Ancef on the day that the wound was closed as prophylaxis, and I think that may have been an infection prior to treatment, if anything, but I think it was really prophylactic treatment.

This is a case that's actually kind of hard for me to interpret even at this point, but they received Diclox, and they received it for a long period of time, and I think this is the individual who actually had a hematoma aspiration the next day, had no erythema, and I think had no temperature increase there but actually grew protease

from the hematoma. So it may well really be an infection, although they list it prophylaxis. And this one had a steroid injection because the mother wasn't happy with the appearance, and never received any antibiotics.

So I think these are for the patients with subcuticular sutures. If you leave this and consider it infected and throw out those three which, at least looking at this and some other spreadsheets, clearly appear not to be infected, you're really left with three infections in the DermaBond group and one in the control group, which makes it more even.

Looking at the group that did not get subcu sutures, that actually is a little difficult because most of the indications appear to be real infections, and most of the time course for the antibiotics appear to be real infections. What we do know is that all the infections are in the laceration patients. None are in the incision patients. So it may have something to do with the ED management of the patients.

Here's the method of decontamination, and you can see that most of them received betadiene, which most of us don't pour into wounds. So I imagine it was just betadiene around the outside of the wound, making me question how well they were cleansed. Then again, I looked

at local anesthesia in these patients, and only one of them received local anesthesia. So I think that if there is an increased infection rate, it's probably related to people getting a little sloppy with wound management, because all the preclinical data clearly support DermaBond being antimicrobial.

I think a very important thing is that people have to understand that the use of tissue adhesives is not an excuse to avoid standard wound care. I think if you just do appropriate wound management, then that issue is probably going to go away.

DR. HOWELL: But it's fair to say we're not sure yet, that the wound cleansing piece is a little gray and we're not sure who was doing what.

DR. HOLLANDER: I can't prove it to you, but I'm very confident. The one case from my institution, when I tracked it back, when the kid came back in, it was clear that it was just sloppy cleansing. Also, I point out that almost all of these are from the same institution, also suggesting, as you talked about investigator diversity, that maybe their practice is just a little worse than other people's practice with respect to cleansing. So I'm very comfortable that that's the answer, but I can't put up data and prove it to you right now.

DR. MORROW: Dr. Galandiuk.

DR. GALANDIUK: I have a question about your follow-up period. How did you decide on the five to ten days and the three months, especially with contaminated wounds? One of the main times of late wound infection is going to be between 14 and 30 days.

The next question is regarding the second group, where you had the sutures as well as the DermaBond. I agree with Dr. Boykin that many times, if you're using subcuticular, you don't need anything else. I close all my abdominal incisions with subcuticular without any other devices, and they heal nice. So you wonder how much DermaBond is really necessary there.

Another thing that confuses me is the mention of 5-0. In one of the wounds that you showed during the presentation, it looked like there was 5-0 closing the wound, and then there was DermaBond on top of that. Does the 5-0 closure apply at all to the second group, or only the first group?

DR. MORROW: I think the question is, is 5-0 for both the subcuticular and the dermal stitch, or is it only for the dermal stitch?

DR. HOLLANDER: I think it's just the dermal stitch that looked at that, and I think your other point

that some wounds can be closed so well with deep sutures that what you do on the surface is probably not quite as important is obviously true. Once again, it comes to the diverse patient population. Most wounds in the study did not have a subcu stitch, and I think probably the majority of them, or close to 50 percent, were from ED urgent care settings. So I think that's a little different than office plastics practice, where your deep suture plays a huge role.

DR. MORROW: Dr. Chang?

DR. CHANG: So my take-home message is if you're in the emergency room -- actually, I would guess most of the patients, if they need the cleansing, would have local anesthetic. If they were incisional, they would have local anesthetic on board. If the patient, for whatever reason, did not have lidocaine or local anesthetic, did any patients -- and this is to you or any clinician -- did any patients complain of pain or discomfort from the heat of the polymerization reaction?

MR. BAREFOOT: I'll call Dr. Bruns to a microphone to address that question, please.

DR. BRUNS: Good morning. My name is Dr. Thomas Bruns. I'm the Pediatric Emergency Medicine Specialist at T.C. Thompson Children's Hospital in

Chattanooga, Tennessee. I'm on the faculty at the University of Tennessee College of Medicine, Chattanooga unit. I was the principal investigator at our site for the DermaBond clinical trial. Closure Medical has paid my way to come here to share with you my experience with the DermaBond adhesive.

Approximately one year following the completion of the study, my wife and I did purchase some Closure Medical stock for our one-year-old son.

Now, to answer the question --

DR. MORROW: That would be good.

(Laughter.)

DR. BRUNS: To answer your question, we did have a few children when the DermaBond was applied to the skin who did say that they did feel the heat of polymerization, but we never had a child complain about burning or an "Ouch, that really hurts" sensation.

DR. MORROW: Thank you.

Dr. Duncan?

DR. DUNCAN: I just have one final question. Did you study the cosmetic outcome when you compared the DermaBond and the subcuticular stitch with the subcuticular stitch and the steristrips at three months? Was there any real difference, or did you study that between the

subcuticular stitch and the DermaBond and the subcuticular stitch and the steristrips? Was there any advantage?

MR. BAREFOOT: There really was not enough enrollment of the use of steristrips to make any statistical assumptions there. It was very low in the clinical study, the number of steristrips used.

DR. DUNCAN: One final question. You said that you excluded patients who had hypertrophy of the skin already, a history of hypertrophy of the skin, and keloid. Maybe 1,000 of those patients, you probably at least came over with several patients that may have had no incisions before. But did you have patients who actually developed keloid or hypertrophy of the skin afterwards with DermaBond? What kind of affect did that have on those particular patients?

MR. BAREFOOT: Dr. Toriumi, could you address that question for us, please?

DR. TORIUMI: Yes. There were three patients that presented with keloid formation. Actually, it wasn't keloid but it was hypertrophic scar when further analyzed. All those patients were the pediatric population patients. One patient, upon further questioning, did have a relative, an aunt I believe, that had a history of hypertrophic scar formation. So I would imagine that when you look at those

numbers of hypertrophic scar formation, they would correlate with -- at least in my experience, they would correlate with what you would normally see in any type of cross-section of that number of incisions.

DR. MORROW: Thank you.

At this point, we're going to break for 15 minutes. There will be an opportunity to ask further questions of the sponsor after the FDA presentation, if you desire.

(Recess.)

DR. MORROW: We're now ready to begin with the FDA's presentation.

MR. WATSON: Good morning. My name is Anthony Watson. I'm going to start the FDA presentation. Clearly, we're talking about DermaBond, a Closure Medical product.

This is the review team for the PMA: myself, the lead reviewer; Dr. Roxy Horbowyj did the clinical portion; Dr. Murty Ponnapalli did the statistical area; Dr. George Mattamal did chemistry, and also the physical and mechanical testing; and Dr. David Krause did the biocompatibility.

I will be discussing a preclinical summary of the PMA. As I said before, I am the lead reviewer. This is what I'll be discussing. You'll have to forgive me if

it seems a little repetitive from what the company did because if I didn't, I wouldn't have anything to talk about.

(Laughter.)

MR. WATSON: I will try to not spend a lot of time on things that the company has already gone over.

I will give a device description. I'll talk about the preclinical studies, specifically the biocompatibility, a few animal studies, and some mechanical and physical testing that was done.

Once again, a description real quick. DermaBond is a sterile, liquid topical skin adhesive containing a monomeric 2-octyl cyanoacrylate formulation and a color additive. On contact with the skin, it polymerizes to form a flexible adhesive that holds together approximated wound edges of surgical incisions and traumatic lacerations.

Now I will discuss the preclinical studies. As the sponsor has already pointed out, they've done a number of studies using varying formulations of cyanoacrylates, specifically N-butyl cyanoacrylate, which I will refer to from now on as 2-butyl cyanoacrylate, and also two cyanoacrylate studies. In addition to that, I wanted to point out that they did do all these studies in accordance

with the Office of Device Evaluation guidance for biocompatibility, and all the core studies that were required of that biocompatibility guidance were done using the 2-octyl cyanoacrylate formulation similar to DermaBond.

The particular types of tests that were done, as mentioned -- the sponsor went into the specifics. I won't go into the specifics, but the cytotoxicity, toxicology study, sensitization, irritation and intracutaneous reactivity, acute systemic toxicity, subchronic systemic toxicity, and genotoxicity. Implantation studies were done. I will talk about some of the animal studies that were done around that. Hemocompatibility and some other studies that were done in the rabbit, specifically pyrogen and primary eye irritation, which was done with the 2-butyl cyanoacrylate. But as I said before, I want to emphasize that the core studies that were required of the guidance were done with 2-octyl cyanoacrylate.

These studies the sponsor has already presented. Again, this was the pig study that compared DermaBond to 5-0 nylon suture. Dehiscence was not observed among sites closed with DermaBond or sutures.

These were the studies that were done before. Again, this was the biomechanical and histopathological

evaluation comparing wound strength of sutures and DermaBond at 7 and 14 days. The histopathological characteristics of the wound healing were comparable between the two groups, and the wound strength was comparable with sutures and adhesive strips as with DermaBond.

Again, this is the last animal study that was done, DermaBond comparing itself to 5-0 suture. Even though it did not exactly show as much strength as the suture, when you applied multiple strokes of the adhesive it showed that it did have optimum strength and it was close to what the suture performance was.

In conclusion, with the biocompatibility and animal studies, we didn't find any significant concerns about safety raised or adverse effects, and any differences in formulations that were used in the studies did not appear to be consequential to the study outcome.

These mechanical and physical tests, we asked the company to do these tests because they had mentioned in their document that they had done autoclave sterilization and dry heat sterilization, and they were going through the process of looking into both of those methods. We asked them to do these tests. These tests are standard ASTM tests for physical and mechanical properties, and they were

modified somewhat to account for the different features of applying an adhesive.

As we can see, the first test is for pressure-sensitive tape. It doesn't quite apply here, so some of the tests were modified to accommodate the use of the cyanoacrylate. We just wanted to see the end properties, comparing the two sterilization methods to make sure that the properties were not vastly different.

We looked at the adhesion strength, the peel adhesion strength, the water vapor transmission. In particular, that was to make sure that the material would not retain fluids underneath; and the tensile properties of thin plastic sheeting, which obviously had to be modified to account for the cyanoacrylate in use.

The company also did some accelerated stability testing, and they also did some real-time testing. The real-time testing was a nine-month stability study which was extrapolated out to one year. They looked at things such as setting time, parity, water content, color, viscosity, and the results of that basically is that it appeared that the material was stable out to one year.

So in summary of the mechanical and physical tests, we didn't notice any significant differences in the material's properties between the two sterilization

methods, and it did appear that the product was stable out to one year.

In conclusion, the preclinical studies do not raise significant safety concerns with respect to DermaBond. We felt that the results of these studies suggest a reasonable assurance of safety to proceed to human clinical trials.

That basically concludes my portion of the presentation. I would now like to introduce Dr. Roxy Horbowyj to present the clinical portion of the presentation.

Dr. Horbowyj?

DR. HORBOWYJ: The slides that I will be following are on the handout that looks like this. It has three per page, along with my notes. My laptop has decided not to cooperate, so we'll be going with overheads. But in case anything isn't clearly visible, this is the handout that will be presented.

I'm presenting the FDA clinical review for this product, DermaBond. I'll be going over the agenda and introduction, going over a little bit about wound healing, the clinical study, and the clinical study outcomes.

Wounds are divided by duration, and depths are acute and chronic, as we know, and superficial, meaning

extending through the epidermis with or without partial extension to the dermis, as well as deep, extending through the dermis. In this case, we're talking about acute wounds with both superficial and deep extension.

Wound closure. The goal, of course, is to have a completely closed, healing wound, with level apposition of the dermal and epithelial edges with minimal or no tension across the incision. The strength of the closure is usually thought to lie in the dermis.

Traditional techniques of closure include primary intention, where the base of the dermis, if open, and the surface of the epidermis are approximated. This technique is faster and simpler than secondary intention, which is contraindicated usually in wounds with foreign bodies, incomplete hemostasis, and infection. In secondary intention, the wound edges, as we know, are left open. Contraction and epithelization approximate the edges. In many cases, good or better functional anesthetic results are obtained for superficial wounds. The third method is tertiary intention.

Devices commonly used and currently available in the United States in order to provide for wound closure include sutures, staples, and adhesive strips.

The device presented here is DermaBond. As you

have heard, it's a liquid 2-octyl cyanoacrylate monomer provided with a D&C violet #2 colorant, as well as plasticizer and free radical reaction inhibitors, as well as stabilizers in a manually crushable glass ampule that's contained in a plastic vial. It's applied to a horizontally placed, dry, decontaminated wound with edges approximated, and by brushing the initiator-containing ampule tip back and forth along the wound edges.

The reaction initiation is anionic. Skin protein amino acid groups are said to participate in the reaction with minor contribution, as opposed to the more active and available hydroxyl anions at physiologic pH.

Polymerization on skin contact is exothermic. It is said to occur over 45 to 60 seconds, to give a flexible film that is to achieve full mechanical strength at two minutes after application. Removal can be by non-tangential shear or by slough with re-epithelialization at five to ten days.

The clinical study, as you have heard, was a pivotal safety and effectiveness study. A separate study was not done to evaluate safety because of the preclinical study results. The study was prospective, randomized, controlled, and ten center.

The objectives from the clinical standpoint

were to evaluate the device performance in terms of safety and effectiveness in the approximation of lacerated and incised skin; to compare device performance with commercially available skin closure devices, namely sutures, staples, and adhesive strips; and then to substantiate device advantage over commercially available skin closure devices.

Statistically, as you've heard, the null hypothesis was that control is better than DermaBond, and the alternative hypothesis was that DermaBond is the same or better than control.

Indications were of two types, surgical incisions or trauma-induced lacerations that otherwise could be closed with non-absorbable 5-0 or smaller sutures, where subcuticular sutures would not be used, and surgical incisions with trauma-induced lacerations that could otherwise be closed with non-absorbable 5-0 or smaller sutures, where subcuticular sutures would be used. So in the first indication it would be 5-0 sutures alone, and in the second indication it would be subcuticular stitch and the 5-0 suture both.

Safety was evaluated looking at parameters of acute inflammation at the five- to ten-day period, with a semi-quantitative 0-3 scale looking at erythema, edema,

pain, and temperature. Wound infection was evaluated at five to ten days per visual evidence at the wound site; wound dehiscence at five to ten days, as well as three months, per visual evaluation; and wound cosmesis at three months per the modified Hollander cosmesis scale you've heard described. Unacceptable adverse cosmetic events and unanticipated adverse events were also evaluated at five to ten days, and three months.

Effectiveness was evaluated by primary and secondary endpoints. According to the protocol, the prospectively identified endpoint was complete, 100 percent apposition at five to ten days. So progress of wound healing at five to ten days for DermaBond is equal to or better than for commercially available adhesive wound closures, non-absorbable sutures, or staples. The retrospective endpoint that was identified by the sponsor was greater than 50 percent epithelial apposition at five to ten days. This was identified retrospectively and analyzed after first analyzing the data according to the prospective endpoint.

The secondary endpoints were defined in the protocol as incidence of need for additional securing devices at the time of initial treatment for DermaBond is equal to or less than that for commercially available

adhesive wound closures -- that is, strips. So the secondary endpoint was not defined to compare DermaBond to suture, staples, and strips, but only to strips.

The time required for treatment for DermaBond is equal to that for commercially available adhesive wound closures, non-absorbable sutures, or staples. The protocol definition is the time required to close the incision or laceration and the time required later to remove the closure device, when applicable. That was the definition for time required to close the incision. So the data presented showing the 190-some minutes as the definition is really not consistent with what the protocol -- the separation is not really consistent. The protocol definition was as it is here.

Inclusion criteria, and these are directly from the protocol, so they include all the inclusion criteria. They are age greater than one year; health without history or recent/concomitant medications for hepatic, renal, or rheumatic disorders, for steroids, immunosuppressants, immunostimulants, beta blockers and anticoagulants; informed consent; and agreement to follow up.

Exclusion criteria were on the basis of patient characteristics and wound characteristics. Patients with ~~significant multiple trauma, peripheral vascular disease,~~

insulin-dependent diabetes, blood clotting disorders, keloid formation, and allergies to cyanoacrylate or formaldehyde were excluded, as were wounds which were burst stellate lacerations due to crush or hard blow, animal or human bite, decubitus ulcers, gangrene, punctures, except for minimally invasive surgery, any wounds on the scalp that were covered by natural hair, a wound that was at the mucocutaneous junction or mucosa, including the vermilion border of the lip, wounds to be closed with U.S.P. 4-0 or larger diameter suture, wounds with visual evidence of active infection, wounds requiring debridement of devitalized tissue or contaminated tissue, and wounds at the site of a rash or skin lesion that would make evaluation of the outcome difficult.

Treatment first required that wounds meet inclusion and exclusion criteria. Random assignment was then to treatment group DermaBond or control. A caregiver then assigned a wound to the non-subcuticular stitch or the with subcuticular stitch study arm. All eligible wounds per patient were treated with the same device group. Decontamination was commonly with betadiene and saline, and approximately 10 percent or so used alcohol or hibiclens, or no decontamination or other forms. Local anesthesia would be applied, hemostasis established by these means.

Closure was performed and a dressing applied. The dressings were non-medicated bandages. That was specified. Topical medications were excluded because DermaBond film permeability by topical medications, oxygen, water, or body fluids is not known and was not addressed in this clinical study.

Follow-up was at five to ten days, and for safety and effectiveness it was three months for safety and otherwise as needed.

Outcome scales for effectiveness. For the additional securing device, it was a yes/no question evaluated at time of treatment. Treatment time was recorded in seconds at treatment time, and the wound healing scale was evaluated at five to ten days. Safety was evaluated by acute inflammation, again looking at these wound characteristics. Suspected infection was evaluated simply by a yes/no question at five days and at three months. Dehiscence was also evaluated by a yes/no question at five to ten days and three months. Cosmesis was by the modified Hollander cosmesis scale at three months.

Wound healing category scale, as you see here, was complete apposition, 100 percent apposition. That was the prospectively defined endpoint. Retrospectively, the sponsor combined categories 1 and 2 and reevaluated the

data. Dehiscence was defined in the protocol as separation of previously apposed edges. However, this definition didn't really address the depth of the wound, because if the wound was very superficial and not really into the dermis, you couldn't really distinguish between simple epidermal separation or separation all the way to the base of the wound if you didn't know the original depth of the wound.

Acute inflammation. This is the scale that was used and, again, erythema and edema were evaluated along wound margins. Similarly, pain and temperature were evaluated along wound margins. The cosmesis scale that was used was a 6-point scale looking at step-off borders, edge inversion, contour irregularities, excessive inflammation, wound margin separation, and overall appearance. These were scored as a yes or no, and overall appearance was scored as a poor or good result.

Suspected infection, again, was evaluated as yes, suspected, or no. The only other item that was recorded in that series was culture taken, yes or no. No other scales or evaluation tools, even if they were available, were used in this study to evaluate suspected infection.

The study population is as presented here. The

group with non-subcuticular sutures is presented to the left here, and with stitch here on the right. There were non-study wounds that were included, but these do not contribute to the safety and effectiveness outcomes. You can see here, as the sponsor presented, the number of patients who completed the study and the comparable percentages of patients lost to follow-up.

The investigational centers, as you've seen, were as follows, of various types, and here are the distributions of the numbers of patients and percentages evaluated per site.

Study arms. The NSS group included full thickness and partial thickness wounds. These wounds in this arm, however, weren't followed for their thickness, meaning it wasn't reported which of these wounds had complete dermal breach and which had partial dermal breach. So we don't know the percentage of each in this arm. This is the number of wounds treated with DermaBond and the distribution of sutures, strips, and staples that were used. As you can see, 80 percent of the wounds closed in this arm were closed with sutures, about 20 percent were closed with strips, and only one wound was closed with staples.

The wounds that were closed in the group

labeled "with subcuticular stitch," in this case, full thickness wounds were converted to a partial thickness wound and then the epidermis was closed. In this case, the distribution of use here, sutures were about 70 percent, strips 27 percent, and in five cases staples were used.

I'll go over the clinical study outcomes now for both groups, addressing first the NSS group and then the WSS group.

This slide addresses all the effectiveness and safety parameters that were used. Here we have the distribution again of the sutures, the strips, the staples. This was the prospectively defined endpoint, and you can see here the percentage of patients in each group which attained the prospectively defined primary endpoint.

Additional securing devices. The percentages are here for the DermaBond group, and since all the contribution came from sutures, which is not consistent with the way the secondary endpoint was defined in the protocol but is here, that was 5.4 percent. But the contribution from adhesive strips, which would be here, was zero.

The mean treatment time, as you have seen, was 189 seconds, and the mean here was 369, but this is the mean of the amount of time that it took to close with

sutures, with strips, and with staples. As you can see, those were various.

Looking at the safety aspects, these were the percentages that were obtained. As you can see, 11 percent erythema with DermaBond, and 33 percent erythema with control. The rest of these are comparable, and what's interesting to note is that in the assessment of pain, the results are comparable also.

These are the outcomes for dehiscence.

The retrospective analysis with the revised primary endpoints gave percentages of 91 percent and 95 percent, as you can see. Thereafter, the logistic regression was performed, and our statistician, Dr. Murty Ponnapalli, will address that assessment.

Looking at the various covariates for the groups, as you can see, baseline demographics, the DermaBond is first and the control is second. The distributions are comparable, and statistically there was no significant difference.

Looking at the gender, race, and obesity distributions, again there were no statistically significant differences.

Similarly, looking at wound dimensions, these were not statistically significant within this group.

However, if you later on compare these numbers to those used in the with subcuticular stitch group, they are different. But within the group, they are not different statistically.

Wound locations were various, and again by statistics, and I think clinically as well, they were not statistically different between DermaBond and control. Similarly, wound types which were evaluated were not statistically different.

What was statistically different was the amount of local anesthesia used with DermaBond compared to control in the non-subcuticular stitch group. However, in the logistic model, as you've heard, this did not contribute the covariates that the sponsor mentioned, which were wound volume, location, and procedure type. So even though this was statistically significant between the groups, the logistic model didn't feel that that was different.

Looking at the overall outcome, then, of safety and effectiveness in this way, you can see that this is control and the upper one is DermaBond, the differences with the different endpoints. This is the prospectively defined endpoint. This is the retrospectively defined endpoint, where nearly all patients are starting to become included, the difference in a secondary endpoint of

additional securing devices, and this is looking at the combination of DermaBond versus strips and sutures and staples, as was presented, although not defined in the protocol: erythema, edema, pain, suspected infection, cosmesis, and dehiscence at any time.

Now, when we looked at this distribution and looked through different groups and looked at the relationships of the different groups between erythema, edema, and suspected infection and dehiscence, with control, even though the erythema is higher, there is usually no correlation with -- not as strong a correlation with erythema. It was usually present much more often than just with suspected infection. But in the case of DermaBond, when you had suspected infection, then the erythema seemed to be more prominent, and dehiscence.

This slide just shows the primary effectiveness endpoint evaluated for these various different subgroups that we looked at, just to see if there was something in particular that was driving an effect. As you can see, in most of these subgroups the results are similar, with control being at the bottom again and DermaBond being on the top.

Looking at the retrospective endpoint, greater than 50 percent apposition, you can see a similar trend

again, and that most patients are starting to become included.

Looking at the additional securing devices, these are the percentages. Again, looking at DermaBond, the distribution with sutures, strips, and staples, and time, and we've gone over these but I thought the visual would be good.

Looking at percent suspected infection, here is the overall comparison. DermaBond again is on top and control is below. This is only from zero to 10 percent. So this is the comparison overall. Then looking at the various subgroups, this has only one line because control was zero and DermaBond was 6 percent. The infections were more so in males, more so in the face. On the hand, control was ahead. Jagged lacerations, this was greater in the DermaBond group. Smooth also.

This is retrospectively analyzed. So from wound to wound, how accurate this is as far as being consistent with complete dermal penetration or partial dermal penetration is difficult to truly say because the dermis, as you know, varies in its location and depth.

Looking at the emergency rooms and urgent care centers, this was the distribution of infection, suspected infection with the non subcuticular stitch group, as

opposed to the non-ER/non-urgent care centers. These numbers here are the numbers per group that were looked at, and when there's an asterisk there, then it was statistically significant.

Looking at the cosmesis in patients with suspected infections, in this group the contribution was really from the lacerations, jagged and smooth, incision, excision, and minimally invasive surgery really didn't have a contribution. So the eight patients or wounds that were with suspected infection were from lacerations, and when we looked to see where they fell for age less than 19, there were six of these patients, and the ages of these patients were two, six, eight, and eleven years old. So they're mostly in the younger of this group.

The cosmetic outcome was about half for these patients. About half the patients had a cosmetic outcome that was less than optimum when they were suspected to have infection.

In the control group, there were two patients who had smooth lacerations who had suspected infection, and their outcome is here.

So that non-subcuticular stitch group addressed partial and complete or full thickness wounds. The with subcuticular stitch in dermis was closed, so it would more

be thought of as a partial dermal penetration. The results are again as follows, comparing the percentage closed with DermaBond compared to control. For the first prospectively defined endpoint, 84.3 percent versus 96.4 percent. Again looking at the use of additional securing devices for the distribution of devices used and the total, and the contribution here. What is being presented is the mean here versus this, and the mean treatment times with the distributions, the control group being there, again recognizing that the 718 is referring to five instances of closure with staples.

Comparing again the acute inflammation that was observed, the percentages are as follows. Again, as you can see, the differences for erythema were different. But as far as edema, pain, temperature were not different. The percentages of suspected infection were 3.6 percent and 1.2 percent, again a several-fold difference, as in the previous group. The cosmesis score, in this case looking at the optimal score, was similar. Then these prospective analyses with the revised endpoints, which then started to include all patients in the groups, 98 and 94 percent.

Again reviewing just the baseline demographics, there were no statistically significant differences for age, nor for any of the other covariates that were shown,

but I'll show them here.

Wound location. Now, these are similar within the group, but as you may remember, in the NSS group the mean length was 1.5 centimeters, the mean width was 2.5 millimeters, and the depth was 5.7 millimeters. Going on further and comparing the covariates of wound location and wound type, there were no statistically significant differences.

Then comparing local anesthetic use for the two groups, in the with subcuticular stitch arm there was no difference as to local anesthetic use.

Here are all outcomes, comparing again the primary endpoints as was defined prospectively, and this was the difference that was observed. The retrospectively defined endpoints, nearly all patients fall into those endpoints. Then looking at the differences in the additional securing devices, this is driven again by the suture contribution, although strips do contribute here.

Here we have erythema, edema, pain, suspected infection, cosmesis score, and dehiscence at any time.

Again, this is just to show that when comparing control and treatment for DermaBond in the different groups, the trends are similar. In this case, this group is very small, six patients for DermaBond and five patients

for control.

When the retrospectively defined primary endpoint is evaluated, then nearly all patients fall into the category.

Looking at additional securing devices that were used, these are the percentages with sutures; with strips; staples did not require any, there were only five; and DermaBond.

Mean treatment time, again as you saw in the chart.

Suspected infections with this group, this is the overall, and again you can see the pediatric age here defined as less than 19 years old. Differences in contribution from race, males, face, body locations basically, smooth wounds as opposed to jagged wounds. Then these numbers here, however, are low. Looking at the contribution from the ER and urgent care centers, and this is the contribution from DermaBond and non-ER and non-urgent care centers. These numbers here are small for the ER and urgent care centers, 19 and 17, so they're not really a big contribution to this whole group.

Cosmesis in patients with suspected infection in this group was, as you can see -- they were mostly from jagged and smooth lacerations in this distribution, and for

control there were none. For excisions and minimally invasive surgery, the distributions were as such. One of the contributions was in the pediatric age, and in looking at the cosmetic outcome that was less than optimal in this group, four out of five, the five infected patients had a less than optimal cosmetic outcome. In the control, this number just wasn't obvious.

This slide puts together both the NSS and WSS groups here. So both the groups that were with partial and full thickness, which would have been the NSS group, and then the wounds here which had dermal closure here, you can see the contributions. The white here that comes across in this slide is the contribution from DermaBond, and unfortunately because it's black and white now, that doesn't show up. But it comes up to -- I guess you can see the black lines right there, so you can read that.

So this is the trend comparing the NSS group and the WSS group. With the retrospectively defined endpoint, the need for additional devices, the DermaBond group being right there. Erythema, edema, pain being equivalent for each of the separate groups; temperature, suspected infection, which here in both groups shows up as higher for DermaBond than for control, which are in between; the cosmesis, and the dehiscence.

I think this allows you to compare the outcomes in the group where there was a mixture of partial and full thickness wounds and a set of wounds where there was dermal closure.

Thank you.

Now I'd like to introduce Dr. Murty Ponnapalli, who will go over the statistical aspects of this study.

DR. PONNAPALLI: In view of Dr. Roxy Horbowyj's presentation, I will present only the primary efficacy endpoints. There will be a little bit of repetition. You'll have to pardon that. Plus, I will describe briefly the design of the trial.

It's a prospective, randomized, controlled study with commercially available devices as control.

Indications: as a stand-alone device or as an adjunct to sutures for wound healing.

Primary outcome measures: complete apposition of tissue or greater than 50 percent apposition of tissue in five to ten days following treatment.

Efficacy criterion: percentage of wounds with complete apposition or percentage with greater than 50 percent apposition.

Now I'm going to get a little technical. Suppose Pe and Pc as the proportions of successes with the

treatment and the control. One way of testing the efficacy is to set up the Blackwelder's hypothesis that the proportion of successes under the experimental device, which is Pe, is less than or equal to the proportion of successes under the control, which is Pc minus 0.08, versus everything else as the alternative. That 0.08, that is the delta that is used. So we use 8 percent as the delta.

Another way of doing this is to use the Cochran-Mantel-Haenszel test for Pe equal to Pc in each of the centers. I want to emphasize here that the Cochran-Mantel-Haenszel test does not depend on the poolability of the centers. It is of value with respect to probability, except the hypothesis has to be Pe equal to Pc, which appears under the second bullet there. That has to be interpreted as the proportions being equal in each of the centers.

The final analysis that is used is logistic regression analysis, with the covariates of surgical procedure; type of wound; body location; length, width and depth of the wound; age; gender; race; use of local anesthetics; the center; and the treatment. This is when the outcome is dichotomized, it's a well-known device to analyze the data taking covariates into consideration.

There are quite a few categories here, the

group with non-subcuticular sutures, the group with subcuticular sutures, with the criterion of complete apposition, with greater than 50 percent apposition, et cetera. The order I'm going to follow is first I'm going to take complete apposition and look at the data. Then I will take greater than 50 percent apposition and look at the data. Finally, the results of the logistic analysis.

This is complete apposition, and the subgroup is NSS, non-subcuticular sutures. The percentages of successes are given in the second row there, the second row and second column corresponding to the experimental device, the second row and third column corresponding to the control device. So the percentage of successes with the experimental device is 75.1. The percentage with control is 88.8.

If you perform the test for the Blackwelder hypothesis, this leads to the acceptance of the hypothesis that the experimental device is inferior. If you perform the Cochran-Mantel-Haenszel test for Pe is equal to Pc in each of the centers -- that is, one single test for Pe is equal to Pc in each of the centers -- that gives P is equal to 0.001. That means we reject the hypothesis Pe is equal to Pc.

I also looked at the 95 percent confidence

interval, which does not depend on the delta that we used. That turned out to be -- the 95 percent confidence interval for Pe minus Pc turns out to be -.21, -.07, or in percentages it's -1 percent and -7 percent.

We're still talking about complete apposition as the criterion, but this time it is the WSS group that we are considering with subcuticular sutures. The P value for the Blackwelder hypothesis turns out to be 0.89, which again leads to the acceptance of the hypothesis of inferiority of the experimental device. The Cochran-Mantel-Haenszel test for Pe is equal to Pc turns out to be again 0.001, and this leads to the rejection of the hypothesis of equivalence of the treatment and the control. The 95 percent confidence interval turns out to be -.18 and -.06.

Now I'll go to the criterion of greater than 50 percent apposition, and the group under consideration is NSS, no subcuticular sutures. The Blackwelder hypothesis gives the P value as 0.06, and this leads to the marginal acceptance of the hypothesis that the experimental device is inferior. The Cochran-Mantel-Haenszel test gives P equals 0.001. This leads to the rejection of the hypothesis Pe is equal to Pc. The 95 percent confidence interval for Pe minus Pc turns out to be -.092, .002. The

endpoint for this interval for the first time turns out to be positive.

Now, again we are considering greater than 50 percent apposition as the criterion, but the group under consideration is with subcuticular sutures. The Blackwelder hypothesis gives P is equal to 0.0001, and the conclusion is that the experimental device is equivalent or better than control in this group. The Cochran-Mantel-Haenszel test for Pe is equal to Pc in each of the centers gives P is equal to 0.557. This leads to the acceptance of the hypothesis that the treatment and the control are equivalent. The 95 percent confidence interval for Pe minus Pc turns out to be -.04, .01. Again, the endpoint is positive, slightly more than zero.

Next I'll go to the logistic regression analysis. I'm not going to give the statistical details, but I'm going to tell you the conclusions. With the criterion of complete apposition in the non-subcuticular sutures, with no interaction terms in the model -- I'm referring to the full model -- the treatment differences are found to be highly significant in favor of the control. But with interaction terms, the differences are not significant.

With the criterion of complete apposition, in

the group of with subcuticular sutures, with no interaction terms -- that is, in the full model -- the treatment differences are found to be highly significant in favor of the control. But with interaction terms, the treatment difference is not significant.

I forgot to mention here that this is with complete apposition as the criterion. What I just said applies to complete apposition as the criterion.

Now let us look at greater than 50 percent apposition as the criterion. In the NSS group, the treatment difference is not significant with or without interactions.

In the WSS group also, the treatment differences are not significant with or without interactions.

Concluding remarks. With complete apposition as the criterion, the treatment is not equivalent to the control either in NSS or in WSS groups.

With greater than 50 percent apposition as the criterion, the treatment is marginally equivalent to the control in the NSS group and equivalent to the control in the WSS group.

My third remark applies to how much reliability we can place on the logistic analysis. The interpretation

of non-significance of treatment difference in the presence of interactions is problematic. It's one of the thorny problems in statistics. It is therefore difficult to interpret the results of logistic analysis. The no-interaction model confirms the results of the 2x2 analyses.

This concludes my presentation.

DR. MORROW: Thank you.

We now have time for discussion by the panel, further questions to either the FDA or to the sponsor, and comments.

Dr. Howell, did you have any comments?

DR. HOWELL: I think most of the comments I wanted to make we've already spoken about. Just in brief, I would say that a couple of concerns that continue to reside with me are, one, concerning this issue of infection. I think we have a group of patients with wounds that are hopefully fairly straightforward in terms of how they were defined and studied. I think with wounds that are more problematic and more prone to infection, that tendency towards infection may be a concern and may need to be followed.

I also wanted to get some clarification, and I guess you wanted to comment also on some of the statistics. That last presentation was interesting to me and I just

wanted to get a sense of how substantive or how much we can really put our faith in the logistic regression model that was utilized.

DR. MORROW: Is that a question?

DR. HOWELL: That's a question.

DR. MORROW: Okay. Could the FDA please try to address more specifically that question of how much faith we can put in the logistic regression model as non-statisticians?

DR. HOWELL: I guess my question really is that my sense was that multiple logistic regression is really thought to be much more of an elegant approach to a problem like this, in the sense that it really accounts for confounders and covariates. But I got the sense that you were somewhat ambivalent about it in your presentation.

DR. PONNAPALLI: In general, it is true that taking covariates into consideration is better than not taking covariates into consideration. But here, what is disturbing here is that you're getting almost opposite conclusions when you introduce interactions. Without interactions, only main effects, there are no controversies and you can test for the treatment effect. That is in the full model.

In the full model, it turns out the treatments

are really highly significant. But when you introduce interactions into the model, there are no significant differences between the treatments. According to my understanding, if the treatments were significantly different, even with the interactions, then you could place a lot of confidence in that. In other words, when you accept the hypothesis with the interactions, there is less confidence. The explanation is how much of the main effect goes into the interactions is somewhat ambiguous in the model. How much to be included in the main effect, what part of it goes into the interactions? That seems to be ambiguous in the model when you introduce interactions. That is why when you accept the hypothesis, you cannot place too much reliance -- in my judgment, you cannot place too much reliance on that.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: I'd like to revisit the comment that I made this morning, and, Dr. Ponnapalli -- is that the correct pronunciation?

DR. PONNAPALLI: Yes.

DR. JANOSKY: If you would, please, I'm going to essentially address the same question that I made this morning. If we looked at your table, which is the very first table you presented to us, NSS -- it might be helpful

if we got that back up again, if that would be reasonable to do. It looks like it was the third or fourth overhead that was presented today.

These are the data that were also presented from the sponsor, and what was presented by the sponsor is if we look in that first row, the device is giving us a percentage of success of 75, and the control is giving us a percentage of success of 89 approximately. So the sponsor came to the conclusion that those were equivalent based on a test of no difference, which is not logical statistically. That's not what we do. We don't show no difference and then conclude equivalence.

What you had done was to actually do a test of equivalence, and thank you for providing that for us. I appreciate that. If you look at the test of equivalence, they're not determined to be equivalent. Matter of fact, control is doing better than the experimental device.

If we look at your very next overhead, we see the same thing. The sponsor again, just to walk through it, is showing that those two are equivalent because they found no difference. Those two tests are logically inconsistent in statistical hypothesis testing. You again did the appropriate test for us, which is a test of equivalence, and it shows that, in fact, control was better

than the experimental condition.

So my question is if we go back to the conclusion that the sponsor had led us down from a statistical perspective we know that's not the right path to go down, are these two equivalent based on these two tables?

DR. PONNAPALLI: It depends on which statistical test you use, and also it very heavily depends on what delta you use. But it was agreed in the submission that one should use 8 percent delta. Also, in fact, it was agreed that the Blackwelder hypothesis that I showed there, it is that that should be tested.

DR. JANOSKY: And a standard within statistical science is what you had used, which is the Blackwelder 8 percent difference.

DR. PONNAPALLI: Yes. But to be sure, I also examined the other possible approaches. You can look at the 95 percent confidence interval again, which applies to all proportions, and you can form a judgment. In case you question the delta, you can base your judgment on the last confidence.

DR. JANOSKY: I'll leave the point for a moment.

DR. MORROW: Dr. Whalen?

DR. WHALEN: It's not really a question, it's more a comment, and I'm not sure this clarifies rather than confounds. But the variable of apposition, to me, there's a lot to be said about it statistically, but as to clinical significance, I think we're trying to make a black and white issue out of not only a gray issue but a gray issue that's so faint as to almost not be seen. I would suggest that the very difficulty that the investigators have had in delineating whether or not there was or was not apposition speaks to the fact that there's very little clinical significance to it.

All of these wounds seem to have been clinically significantly apposed whether or not we put that into little 2x2 boxes or not. To me, I think we're making a big mountain out of a little mole hill.

DR. MORROW: Dr. Biros?

DR. BIROS: On that same line, I would wonder from the sponsors about which wounds needed retreatment. How many wounds that didn't completely appose needed anything further?

DR. MORROW: Could someone from the sponsor address that?

Perhaps while we're hunting that up, Dr. Burns

DR. BURNS: I had a couple of questions. One is, is there potentially a difference in the ability to actually see the wound? If you have it covered with the cyanoacrylate adhesive, is it harder to judge whether it's closed versus if there's nothing there and you just have it closed with sutures? Is that potentially what could account for differences there? And is there a way of testing for that? And have you done that?

DR. HOLLANDER: I think that's the really important point here, and I think I tried to illustrate that by the slide I showed earlier. At the time of the five- to ten-day follow-up, it is difficult to discern whether there may be minimal degrees of apposition. We kind of believe that if it was totally dehisced, that would be kind of obvious and anybody could pick that up, which is why we kind of lumped together the complete apposition with the less than 50 percent apposition, because just clinically it's intuitive that if 75 or 88 percent of the wounds had totally apposed, then the ones that are not apposed should have a minimal degree of separation since most come together fine, and clinically that's what we observed.

But it's very hard to determine, for example, in the slide that I showed, whether or not there's 100

percent apposition or 70 percent apposition. There's an area that you have the adhesive over that you just can't tell, and I think that's why that as an endpoint is very soft and not clinically meaningful, because the three-month data was very well matched.

DR. BURNS: I was going to ask, if there really was a difference there at the five- to ten-day period, would you have expected to see the cosmesis that you saw at three months? Because there, there was clearly no difference.

DR. HOLLANDER: I suspect there really is no clinically meaningful difference at the five- to ten-day period, because it's hard for me to believe that if there is a 75 percent separation, they're all going to look the same three months later. So I think if there is a difference, it's probably very small, and it's certainly not clinically meaningful because it didn't impact the long-term outcome at all.

DR. BURNS: One other point, because I had two questions. The other was that earlier in the day we heard about a linear regression or a regression analysis model, and I was unclear where that came from, who had suggested that be done, because I thought that came from the FDA.

DR. HOLLANDER: Yes, that was suggested by the

FDA, and actually the covariates that were put in the model were suggested by the FDA. When that was done, as you saw, everything kind of fell out in the wash and there was no difference. So I think I'd echo Dr. Whalen's comments that we're trying to figure out statistics about something with not a whole boatload of clinical meaning, but the suggestion to reanalyze it that way was generated from the FDA.

DR. MORROW: Did you have an answer to that previous question about wound retreatment?

DR. WEST: David West, regulatory consultant to Closure Medical.

I believe the question was if there was less than complete apposition, was there retreatment? And the answer is no. The degree of apposition at five to ten days was noted, and the wound was followed to three months. So the outcome evaluation at three months was on all wounds whether or not there was any degree or lack of apposition at five to ten days.

If wounds frankly dehisced, they were considered a frank failure of either the suture or DermaBond. So they were considered as failures. Does that answer the question?

DR. MORROW: Yes.

Dr. Chang?

DR. CHANG: I was impressed that Dr. Toriumi had no dehiscence with 111 patients. Were any of the clinicians who might have had other results, what were the indications for additional securing devices at the time of wound closure? Or if Dr. Toriumi had other additional securing devices, what was the indication? What would make you think that you needed extra suture, staple, or steristrip?

DR. MORROW: You were referring to in the sutured arm of this trial?

DR. CHANG: Yes, right.

DR. TORIUMI: Yes, it's accurate that I did not have any dehiscences in my experience. But again, it's a very controlled situation with incisions being made. There were some traumatic wounds which were treated and we had no dehiscences.

There are some things that can be done. In fact, one of the investigators from Canada has talked about -- not included in this study, however -- has talked about using steristrips to aid in bringing the edges together, and then in certain areas tacking sutures or tacking strips along the wound, then apply the DermaBond, and then remove those sutures or strips to complete the closure. So there

are things that can be used to aid the closure, but the primary use is that of a forceps which is just applied to the epidermal skin edge to create a degree of eversion, and then at that point apply the DermaBond. Using that technique, we've been very successful in getting complete apposition of the edge.

Just to interject one other point, I agree with many of the panelists here that have mentioned about the seven- to ten-day time period when we're talking about the wound edge apposition. I think the bottom line is that as clinicians, we all know that it's your final outcome. When we look at the final outcomes in this study, it's really very interesting to note that they're equivalent. When I did my one-year follow-up on our data, it happened to show that our data was quite excellent in favor of the DermaBond. If you're interested in that data, at some point in time I could just flash it up.

DR. MORROW: Further questions?

(No response.)

DR. MORROW: If there are no further questions at this point in time, we will move on to the FDA's questions to the panel. Let me remind you that these questions do not constitute a vote. They merely constitute your opinion on this specific issue.

DR. WITTEN: Dr. Morrow, before you move on to the questions that we had previously formulated, I wonder if based on this discussion I could ask one question before these questions.

DR. MORROW: Why, sure.

DR. WITTEN: And that would be the following. I heard some comments, particularly from Dr. Whalen and others of you also, regarding the gray area because of the endpoint at five to ten days and how you should look at it. I wonder whether any of the panel members have any comments on what they think would be the most important things for us to focus on in looking at the study to determine what clinically meaningful differences or similarities there were between the treatment and control.

DR. MORROW: Okay. So the first question we'll address is, what is a clinically relevant difference between the treatment and the control?

DR. WITTEN: Well, what I really mean to say is, there were many endpoints measured in the study -- not just at five to ten days, but they also looked, for example, at cosmesis, dehiscence. Are there other things that we should be focusing on as important?

DR. MORROW: Okay. You mean other things other than what was addressed in this PMA, or the other things

that were addressed?

DR. WITTEN: No, no. Things that were measured in the PMA that perhaps would make it clearer to us how we should look at the outcome of the device, since as Dr. Whalen mentioned, looking at this issue of five to ten days and 50 percent apposition versus 100 percent apposition, there are some gray areas there that were raised.

DR. BURNS: Is this an additional question to the panel, then, in addition to what we have here?

DR. WITTEN: Yes. I didn't write it down. I'm just asking it right now.

DR. MORROW: So this question basically is, what do you consider clinically relevant about the data in this trial that has been put in front of you?

DR. WITTEN: Right.

DR. MORROW: We will poll the panel. Please briefly state the reasons for what you're saying.

Dr. Boykin, we'll start with you.

DR. BOYKIN: I believe the factors that are most important to me concerning the application of this device are obviously the long-term cosmesis, the incidence of dehiscence in the early follow-up, and the rate of infection. I think the reasons are fairly clear. If we're comparing this to a known mode of application of closure,

these are the things that would make it clinically either acceptable or unacceptable in practice.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I think, on their categorization of wound healing, that category 1 and 2 are not significant and should be grouped together, and only look at categories 3, 4, and 5. Under acute inflammation, the first three categories are insignificant clinically, as well as under edema, the first three categories are insignificant clinically, as well as the first two of the temperature things. I think a lot of things they're looking at aren't important in terms of clinical significance.

DR. MORROW: So what would you say is important in terms of clinical significance?

DR. GALANDIUK: Wound dehiscence and infection.

DR. MORROW: Okay.

DR. JANOSKY: I echo Dr. Boykin's response.

DR. MORROW: Dr. Biros?

DR. BIROS: I guess from my clinical perspective what would be most important is the infection rate. I also think the effectiveness in my definition would be whether or not you need to do anything more with these wounds in the short term. Also, another important

clinical perspective would be the time and convenience, not only to the caretaker but also to the patient.

DR. MORROW: Dr. Whalen?

DR. WHALEN: I'd briefly echo Dr. Boykin. The three-month cosmetic result I think is the single most important, and I think we do need to pay some attention to infection rate.

DR. MORROW: Dr. Chang?

DR. CHANG: I agree with comments made by Dr. Boykin, and we also should pay attention to our patients' desires and their very ready acceptance of not having sutures externally.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: Basically, just the long-term outcome as far as the cosmesis is concerned is number one, and number two, the number of times you have to use an additional securing device in addition to the DermaBond would be of interest to me.

DR. MORROW: Dr. Howell?

DR. HOWELL: I'd say three-month cosmesis, need to use antimicrobials to treat infection, and the need to use additional securing devices at the first closure.

DR. MORROW: Ms. Brinkman?

MS. BRINKMAN: I agree also that the long term

outcomes, and also the fact of the relevance to the patient and their acceptance of this device.

DR. MORROW: Dr. Burns.

DR. BURNS: As somebody who has some ugly scars from being a kid, I think the long-term cosmesis is certainly very important.

DR. MORROW: Dr. Witten, I think you have the feeling of the panel that there is agreement that long-term cosmesis is a primary clinical endpoint, that infection and the rate of complete dehiscence are also relevant, and that other considerations less unanimously considered were the need for additional securing devices, further treatment, and patient convenience and acceptance.

DR. WITTEN: Thank you.

DR. MORROW: Are there any other questions you'd like to ask before we move on to the written questions?

DR. WITTEN: No, thank you.

DR. MORROW: Okay. The written questions, and I think -- be my guest, you can read the written questions.

MR. WATSON: Okay. I'll just read them exactly as they're written.

Question 1 regards effectiveness. "The sponsor utilized a 5 point scale to measure the primary

effectiveness endpoint of progress of wound healing at five to ten days. The scale was as follows: complete apposition; complete apposition with less than 50 percent epidermal separation; incomplete apposition with greater than 50 percent epidermal separation; incomplete apposition with less than 50 percent wound dehiscence down to original depth; incomplete apposition with greater than 50 percent wound dehiscence to original depth; where dehiscence was defined as separation of previously apposed edges.

"Based on this scale, the sponsor tested the null hypothesis that DermaBond was worse than control for complete epidermal closure at five to ten days post-treatment. The sponsor was unable to reject the null hypothesis -- for WSS, P is equal to 0.8991, and for NSS, P is equal to 0.9458. The sponsor then reanalyzed the data based on the null hypothesis that DermaBond was worse than control for complete apposition and incomplete apposition with less than 50 percent epidermal separation, combining the first two categories on the scale above. This reanalysis allowed them to reject the null hypothesis.

"The sponsor cited imprecision of the scaled scoring criteria and the lack of familiarity of investigators at examining wounds sometimes covered with remnants of polymerized adhesives as the reasons for

failure to reject the null hypothesis in the first analysis.

"The sponsor then conducted a third analysis at the request of the FDA using a logistic regression method. This analysis demonstrated that for selected covariates -- for example, investigational site, anatomic location, wound characteristics, et cetera -- the differences in complete apposition are not statistically different between DermaBond and control."

Here's the question, part A. "Because the same scale was used to evaluate both treatment and control arms, and the patients in both arms were randomized and therefore may be considered comparable, is it possible for scale imprecision to account for the failure to reject the null hypothesis in the first analysis?"

Part B. "Which success criterion is more appropriate for the efficacy of the device: (i) Complete apposition or (ii) complete apposition or incomplete apposition with less than 50 percent epidermal separation? If (ii), how would this change the indications for the device?"

DR. MORROW: I think we may have addressed this question to some extent in our comments about this particular scale before, but I guess for completeness sake

we'll do that again.

Before we do that, could I just ask the sponsor one question? Could you please clarify for me how many patients in the treatment and the control groups who did not have an infection had a complete wound dehiscence?

And maybe while you're hunting for that, we can start polling the panel members on the question that's on the table before us, if you don't have that data.

Dr. Burns, regarding the treatment scale, is it possible for scale imprecision to account for failure to reject the null hypothesis? That's Part A.

And Part B, which of these criteria do you consider most appropriate for efficacy determination?

DR. BURNS: Well, for Part A, as I stated earlier, I think that the imprecision in assessing wound closure is possible because of the presence of the material, that it could easily be mistaken, and that it could eventually affect the failure to reject the null hypothesis.

On the second point, I'll defer to my medical colleagues on what's clinically more appropriate there.

DR. MORROW: Ms. Brinkman?

MS. BRINKMAN: I'm going to defer to all of you on both of these points. Thank you.

DR. MORROW: Dr. Howell?

DR. HOWELL: I'm being deferred to, I guess. I would say this whole area is muddy. One, I think that the clinical assessment is problematic, as we've heard. I think the scale itself was not validated, so that adds some randomness to what's going on. But I do think, again, as we've said, that this is what happens at five to ten days. I think what happens at three months is more important.

DR. MORROW: So your answer to Question 1 is, yes, the imprecision of the scale could account for this?

DR. HOWELL: It could, and I think in the best of all -- I would say yes to that, and in the best of all worlds, I would say that the latter approach -- in other words, combining complete apposition and less than 50 percent dehiscence as one side of a dichotomous outcome variable -- would make sense. But again, I think this is pretty muddy clinically.

DR. MORROW: Okay. Dr. Duncan?

DR. DUNCAN: I agree. I think that it's pretty much a gray zone. I still have some question in my own mind as to what this 50 percent is all about, and what objective scale 50 percent is actually used on. Is it millimeters of separation, or what kind of tools are used to measure this 50 percent in the first place?

The second portion I'll defer on.

DR. MORROW: Dr. Chang?

DR. CHANG: Yes to Question A, Roman ii for Question B, and no change for indications for the last part of the question.

DR. MORROW: Dr. Whalen?

DR. WHALEN: A, yes. B, I would say complete clinically acceptable apposition.

DR. MORROW: Okay. Dr. Biros?

DR. BIROS: I would agree with Dr. Chang.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: The randomization should have taken care of the two issues for the first one. One of the clinical experts today told us that there might have been some confusion with the device placed on top, so that group might have had more imprecision than the group that did not have the DermaBond placed. So in that respect, I would say that perhaps the imprecision was different between those two groups, and we did see some kappa data presented in terms of reliability, which was not particularly impressive. So I think there is great imprecision and unreliability in the assessment.

For the second question, I defer.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I would say no to the first question, and complete apposition for the second.

DR. MORROW: And Dr. Boykin.

DR. BOYKIN: I'd say yes to the first question, and I actually would have changed the entire scale for Part B to something along the lines that Dr. Whalen indicated, normal healing versus abnormal, with some guidelines. I would have eliminated incomplete apposition less than or greater than at five days.

DR. MORROW: Dr. Witten, I think there is the strong feeling of the committee that imprecision in this scale could have been responsible for the results that were seen, that we don't particularly like this scale in general as a clinically relevant measure, and that the long-term evidence of wound healing is the appropriate measure.

Moving on to Question 2.

I'm sorry. Do you have an answer to that other question? Why don't you just tell us that, and then we'll do Question 2.

DR. HOLLANDER: I'm actually sort of going through a table as I give you the answer, so I apologize for being a little slow.

There were a total of 13 dehiscences in the absence of infection. Six of those were in control

patients, seven of those were in DermaBond patients. That's combining both the subcu and non-subcu groups.

Briefly eyeballing it, the reason -- and actually, six of them were in incisions and seven were in lacerations. So it's about equal in both of those respects.

The list of reasons for the dehiscence that happened -- and I'll just read you the list for each of the cases: patient vomited, causing wound dehiscence; steristrips came off; a baby kicked the incision, causing dehiscence; somebody with a large abdominal girth and more tension, and that was a control patient. Those were all control reasons.

DermaBond reasons were non-compliance with wound care instructions in four cases. Three of them were related to excessive bathing and moisture on the wounds. One of them was a 2-year-old child who picked the glue off. In one case, the tissue adhesive just fell off. In two cases there was new or repeat trauma, causing opening of the wounds. I case actually three cases due to new or repeat trauma.

So it's pretty even in both groups with repeat trauma or moisture in the DermaBond group. That's the explanation.

DR. MORROW: Thank you.

Are we ready to move on to Question 2?

MR. WATSON: Question 2 relates to increased infection rates in treatment groups versus control groups. "The results of infection in the clinical trial for the treatment and control groups are given in the table below."

You can see the chart, but just in case, NSS group says treatment is 3.6 percent, control is 0.9 percent. For WSS, the treatment is 3.6 percent and the control was 1.2 percent.

I have to apologize for the slide. I expanded the font and it messed up the word "treatment."

For the question, Part A, "Is this difference in infection rates clinically significant?"

Part B, "If so, how should this issue be addressed in the labeling for the device?"

DR. MORROW: Okay. First please address if you think it's clinically significant. If you say yes to that, then answer Part B.

Dr. Boykin?

DR. BOYKIN: I believe that the numbers that we have to review here show clinical significance. Obviously, as you divide the groups and find subsets, there are some that are not. But the overall group, especially if you

look at all of them beyond the age of 19, which is most of your population, they are significant.

I think that in addressing this as a labeling issue, it should be made clear that this should not be used on contaminated wounds.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I don't believe it's clinically significant.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: I believe that it is and it should be addressed in labeling.

DR. MORROW: In what way?

DR. JANOSKY: Along the lines that Dr. Boykin had suggested, and the standard of care being reiterated.

DR. MORROW: Dr. Biros?

DR. BIROS: Because I think there was sort of a poor understanding or a poor definition of what a wound infection was in the groups that we saw earlier this morning, I don't think there was a significant difference in clinically important infections.

DR. MORROW: Dr. Whalen?

DR. WHALEN: The one comment I would make is that when there was a significant number of the patients, obviously in both treatment and control groups, who were

lacerations, traumatic lacerations presenting to an emergency room, that the control group infection rate is remarkably low, at 0.9 percent and 1.2 percent. Nevertheless, the statistical difference is there, and I think it has to be acknowledged as such, and it is clinically significant. I'm not sure it should be anything as strong as closer monitoring for infection with use is in order, but it certainly deserves attention.

DR. MORROW: Dr. Chang?

DR. CHANG: My impression from the data that was given, and it might have been from one center, they forgot about proper wound care. So in terms of the presentation earlier this morning, it appeared that many of these infections occurred in traumatic lacerations where no local was used, and we can infer that perhaps the wounds were not irrigated and cleansed to clinical standard of care. So statistically the numbers appear to be significant. Is it clinically significant? For the patient that got the infection, probably. Is it significant in terms of passing or not recommending approval? I don't think so.

So the answer is clinically significant, yes, taking the literal view, with my comments in mind. How should this be addressed in the labeling? Probably a

precaution to remind clinicians that use of this adhesive is not placing an antibiotic in the wound, and a reminder that just because it's a glue and you're not putting sutures in, that one should not forget the principles of giving the patient pain relief and adequate debridement and irrigation.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: I don't think the criteria that they use as far as clinical infection rate warrants that this is -- there's a difference as far as being clinically significant. So my answer to Part A is no.

DR. MORROW: Okay. Dr. Howell?

DR. HOWELL: A, yes. B, the label should go to adequate cleansing of the wound.

DR. MORROW: Let me just point out, to clarify any confusion in looking at these numbers, that the 3.6 versus 1.2 percent is not a statistically significant difference. I think someone just stated in discussion that it was, and according to the FDA document that I'm looking at, that was not the case. I believe that is also true for the NSS group, although I can't seem to find the right piece of paper. Is that correct?

PARTICIPANT: That's correct.

DR. MORROW: Okay. So just to make that clear

to the panel members, these differences are not statistically significant. They are numbers.

Who were we up to? Ms. Brinkman?

MS. BRINKMAN: For A, no. But I still think there needs to be a reminder to adequately prepare the wound prior to treatment.

DR. MORROW: And do you think that's an obligation of the sponsor of this product?

MS. BRINKMAN: I don't know if it's an obligation, but it certainly would be a good idea.

DR. MORROW: Okay. Dr. Burns?

DR. BURNS: For A, I think no, because of the issue of non-statistical significance, and also in light of the fact that when you look at acute inflammation, if anything, it favored DermaBond.

For B, I believe that the sponsor already has something in the label for the product not to be used in the presence of a contaminated wound.

DR. MORROW: Dr. Witten, the panel is basically evenly divided on whether or not these numbers represent a clinically significant difference in infection.

Question 3.

MR. WATSON: Question 3 relates to use of additional securing devices with DermaBond. For

clarification, I'll read the chart. Under NSS in the treatment group, that's 5.4, and that's in percent need for additional securing devices. Under control, 6.8 for sutures, zero for adhesive strips, and zero for staples. The WSS group under treatment is 1.2 percent, control is 7.8 percent for sutures, 4.4 percent for adhesive strips, and zero for staples.

"Additional securing devices were used with DermaBond in some instances. The prospective secondary endpoint was to compare the need for additional securing devices between DermaBond and adhesive strips. The data given compares DermaBond to sutures and adhesive strips. Realizing that the intended use of DermaBond is to hold apposed edges together, the impact of additional device use with the product on the study results is unclear.

"Please comment on whether there is a significant difference in the need for additional securing devices. If so, please comment on how this should be addressed in the labeling."

DR. MORROW: Is the intent of this question clear to all the panel members who will be addressing it? Because it's not clear to me. So perhaps whoever from the FDA wrote this could explain to us exactly what you're looking for.

DR. WITTEN: I think that one of the benefits that is claimed for the product is reducing the need for additional securing devices. So we are presenting this information and asking whether this is a clinically significant difference, and how we should represent it. I think some of the panel members alluded to this in their discussion when they asked about whether it was compared to adhesive strips, for example, or whether it was compared to sutures. So we're presenting that information broken down by types of control devices.

DR. MORROW: Okay. Dr. Burns?

DR. BURNS: Based on the information I see here, I don't see that there's any difference between the control and the treatment. If anything, in the WSS group, it favors the treatment.

DR. MORROW: Ms. Brinkman?

MS. BRINKMAN: I agree with Dr. Burns.

DR. HOWELL: Agree.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: As far as I'm concerned, I don't think that there's a difference with the numbers that I actually see here.

DR. MORROW: Dr. Chang?

DR. CHANG: No significant difference, and

there's no need to address this in the labeling.

DR. MORROW: Dr. Whalen?

DR. WHALEN: The reason God created steristrips for pediatric surgeons was to hide the wounds from the parents.

(Laughter.)

DR. WHALEN: So I would always use them. But I don't see it as necessary for the security of the wounds.

DR. MORROW: Thank you. Dr. Biros?

DR. BIROS: I agree that there's no difference.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: No need to address it in the labeling.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I don't think there's a difference, but it's very hard depending on where your wound is. If it's a point of a lot of flexion, like on the top of the knee, you might want to secure it. So I don't think just taking all wounds you can make a statement about this.

DR. MORROW: Dr. Boykin?

DR. BOYKIN: I would say no.

DR. MORROW: There is a unanimous opinion of the panel that this is not an issue that needs to be

further addressed.

MR. WATSON: Question 4 relates to DermaBond indications for use. "The device indications for use state, 'DermaBond adhesive is intended for topical application to hold closed approximated wound edges of trauma-induced lacerations or incisions, including punctures from minimally invasive surgery, that otherwise could be closed with sutures of U.S.P. size 5-0 (1.0 metric).'" The last part there, "or smaller diameter," that really is an objective of the study, and that last sentence should be struck, that last portion of the sentence.

"Based on the data in this PMA, is this a clinically appropriate indications for use statement for a topical closure device?"

DR. MORROW: Okay. If we could go through and see if we think this is an appropriate statement. If you do not believe this is an appropriate statement, could you please offer some guidance as to what would be a better statement?

Dr. Boykin.

DR. BOYKIN: I believe that it's acceptable the way it's worded. Obviously, we could spend a lot of time trying to refine it, but I think it's acceptable.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I don't think it's acceptable because I'm confused with the 5-0 suture, and I would make a statement of wound depth such as 6 millimeters, or some kind of reference, because I think a physician that doesn't do surgical care would basically not know which wounds to treat with this and which not.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: I would place some qualifications on it in addition to the one that was mentioned, namely the one about wound depth. There were also some other things that we had seen in terms of -- I don't know if indications for use would include patient age. If so, those types of issues. I think the age stated was age 2 and above, if I remember correctly.

DR. MORROW: It was 1.

DR. JANOSKY: One and above. So some of those other indications that were mentioned.

DR. MORROW: Anything else beyond age that you had in mind?

DR. JANOSKY: If I would review those, I would surely come up with some. I don't have it in front of me, but there were some other limitations of the patients going in, inclusion and exclusion criteria that were presented.

DR. GALANDIUK: That would be on the immunosuppressants.

DR. JANOSKY: Right, those types of issues. I don't know if you would want it directly in this single statement of indications for use, but at some point those could be addressed.

DR. MORROW: Dr. Witten, maybe you could give us some clarification about how much detail.

DR. WITTEN: I think what we are really asking in this question is whether you have anything to say about the description of the types of wounds rather than about the patient population at this point. So if you could just comment on the description of the wounds that you get from this indications for use statement, and if you have any modifications of that. Of course, there were two studies, a WSS and an NSS study. If there's anything related to those two different studies that would cause you to amplify this or clarify this proposed labeling regarding the wounds themselves.

DR. MORROW: Dr. Biros?

DR. BIROS: I guess I would add to this, "closed approximated wound edges of non-contaminated, very well cleaned, trauma-induced lacerations."

DR. MORROW: Dr. Whalen?

DR. WHALEN: I find it clinically appropriate.

DR. MORROW: Dr. Chang?

DR. CHANG: I think the present label or the indications are fine as written.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: I think that the characteristics of the wound and the location are important. I could probably close an abdominal laparotomy with a 5-0 suture, but that doesn't make it the correct way to do it. I think you have to take into account the characteristics of the wound more so than the size of the 5-0 suture.

DR. MORROW: So by characteristics of the wound, you mean wound size, wound depth, wound location?

DR. DUNCAN: Absolutely.

DR. MORROW: Dr. Howell?

DR. HOWELL: I would agree with the description made by Dr. Biros. I think there's a disconnect between the exclusion criteria and the term "trauma-induced lacerations." But I don't know how best to get at it. So I think the way Dr. Biros referred to it is most appropriate.

DR. MORROW: Ms. Brinkman?

MS. BRINKMAN: I think it's appropriate. I don't know of a better way to describe it.

DR. MORROW: And Dr. Burns.

DR. BURNS: I also think that it's appropriate.

DR. MORROW: We have again a fairly even split of the panel regarding the appropriateness of this language. I think that you've heard that the concerns are that the selection of a suture material is subject to some variability and that a description of the wound characteristics might help to clarify this for a larger group of physicians than were involved in this initial study.

That concludes the questions. Are there any final questions that have come to anyone's mind for the sponsor?

(No response.)

DR. MORROW: If not, does the sponsor have any final statements that they would like to make prior to the voting?

(No response.)

DR. MORROW: Does the sponsor have any final statement that they would like to make prior to the voting?

(No response.)

DR. MORROW: This is usually a yes/no answer.

(Laughter.)

DR. HOLLANDER: We'll make it a yes. Actually,

we spent a lot of time debating that last labeling issue, because it is kind of unclear, and some of the cases where there were little complications in the trial may well have been related to selection of a 5-0, which was pushing the limits for study inclusion. And there is no way to break it down by depth or length or size or body location for the whole variety of wounds that you see.

I think it's pretty clear to me that size itself is not relevant. There's a study not part of this trial but also out of Canada on EMT surgery with patients who had thyroid surgery and 14 to 20 centimeter scars, and with a good subcuticular closure, they healed up fine. I think the real issue is are the skin edges, the epidermal edges, the dermal edges easily apposed at the point you're going to apply the tissue adhesive? And I think if you can do that without subcuticular stitches, that's probably okay. If you do that with subcuticular stitches so it looks like some of the pictures that Dr. Toriumi showed, that's probably okay too.

So if I had to try to get one condition that you would need to make sure this is going to work well, it's to have the skin edges apposed at the time of tissue adhesive application. Dr. Toriumi has a couple of slides that can illustrate exactly what we're talking about so you

can see.

DR. MORROW: We don't need to see any slides. We're in the final comment mode.

Okay, we're ready for voting instructions.

MS. GANTT: Okay. I'm going to read quickly the voting instructions. There are three options: approvable, approvable with conditions, or not approvable.

Approvable is if you vote that the PMA is approvable, you are saying that the FDA should approve the PMA with no conditions attached.

Approvable with conditions. If you vote for approvable with conditions, you are attaching specific conditions to your recommendation that FDA approve the PMA. The conditions must be specified with the motion when approvable with conditions is made. In other words, you may not vote for approvable with conditions and then determine them. Examples of pre-approvable conditions are changes in the draft labeling and resolution of questions concerning some of the data. Examples of post-approval conditions are postmarket studies and submission of periodic reports.

You should propose the extent of the conditions of approval, such as the number of patients to be followed and/or the number interval and type of report to be

considered. In all cases, you must state the reason or purpose for the condition.

The third option is not approvable. It is a benefit-to-risk ratio. The valid scientific evidence used to determine the safety of a device must adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

The process begins with a motion from a member of the panel. It may be for any of the three options, recommendation for approvable, approvable with conditions stated, or not approvable. If the motion is seconded, the chair will ask if anyone would like to discuss the motion and so forth.

Please remember that the proceedings are taped for later transcription. Nonverbal signals are not captured on tape. If you wish to second, please state so rather than waving your hand or holding your hand up or whatever.

You may vote yes, no, or abstain. A majority vote carries a motion.

The voting members for today's panel are Dr. Biros, Dr. Boykin, Dr. Chang, Dr. Duncan, Dr. Galandiuk, Dr. Howell, Dr. Janosky, Dr. Whalen, and Dr. Morrow. The

acting chairperson votes only in the case of a tie.

DR. MORROW: Was there a question regarding the voting instructions?

(No response.)

DR. MORROW: Hearing no questions, is there a motion from the committee? Dr. Chang?

DR. CHANG: I move that the panel advise approval of this PMA with the condition that a reminder be made in the package insert to clinicians along the lines that adequate cleansing of even apparently clean traumatic wounds should be performed with appropriate anesthetic to avoid increased risk of wound infection.

DR. GALANDIUK: I second the motion.

DR. MORROW: We have a motion and a second. Is there discussion of the motion?

DR. GALANDIUK: I would also recommend putting the condition in that they add to the indications superficial wounds not extending to the fascia. That way if it would be a deeper wound, it would have already been closed with some other suture, and I think that would be a better way of restricting use.

DR. MORROW: So we have a motion for approval stating --

MS. GANTT: I'm sorry, it's an approvable with

conditions.

DR. MORROW: Approvable with conditions stating that the labeling will include a reminder for adequate cleansing of even apparently traumatic clean wounds, clean traumatic wounds using local anesthesia and other appropriate measures, as well as the statement that this device is intended for use in wounds which do not extend to the fascia in the absence of other closure. Was that what you said?

DR. CHANG: Is there another way to clarify that to say that one should use subcuticular sutures if it is full thickness?

DR. GALANDIUK: Yes, but you don't have to if you have a very superficial or partial thickness wound. You don't want to have to use suture for it. I mean, you'd love to include that at the time of your closing, the thing you're putting DermaBond on is not to the fascia.

DR. MORROW: Further discussion of this issue?

DR. CHANG: The discussion is just that it may be ambiguous that a clinician may see a full thickness wound down to the fascia and say, oh, I can't use DermaBond because it says don't use that.

DR. GALANDIUK: That probably is not a bad thing.

DR. BURNS: Just a comment from me looking at the labeling, I think that's actually already in the label. It's for application to the skin and not below the skin to the fascia.

DR. MORROW: Could we see the label, what the current statement is?

DR. GALANDIUK: The whole 5-0 thing I think is just incredibly confusing as to what you need this on. The only thing I think is that you should put some kind of label so that physicians or nurse practitioners, whoever is using this stuff, will not use it as the sole method of closure for wounds without any kind of support underneath, for deep wounds.

DR. HOWELL: Why not just say that? That's pretty clear.

DR. MORROW: "DermaBond should not be used as the sole method of closure for --

DR. HOWELL: And is not intended to replace supporting sutures underneath the skin, something like that. That sounds clearer.

DR. MORROW: "DermaBond is not intended to replace suture closure beneath the skin when clinically indicated."

Is there further discussion?

(No response.)

DR. MORROW: The motion and second on the floor now stands for approval with the condition that a reminder that adequate cleansing of even apparently clean traumatic wounds using appropriate local anesthetic and technique is indicated with this product, and that DermaBond is not intended to replace suture closure beneath the skin when such closure is clinically indicated.

Is there any further discussion?

(No response.)

DR. MORROW: Okay. In that case, it's now time to vote. We will first attempt to hand vote. If the voting is unanimous, that will suffice. If it is not, we will then revert to a personal vote.

Will all those in favor of the motion raise their hand?

(Show of hands.)

DR. MORROW: All those opposed?

(No response.)

DR. WITTEN: I think we still need to have a --

DR. MORROW: We're going to do that.

We appear to have a unanimous vote in favor of approval with the conditions as stated.

I now need to go around and ask all the voting

members to please state why they voted as they voted.

Dr. Boykin?

DR. BOYKIN: I believe that the information we've been presented with demonstrates that the device is safe when properly applied using the appropriate evaluations that we would use for other techniques.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I would also vote for approval with conditions. I think the device is safe.

DR. MORROW: Could we please have quiet in the room?

DR. GALANDIUK: I think the device is safe. It's a shame that the statistics were such a shambles.

DR. MORROW: Dr. Janosky?

DR. JANOSKY: I voted for approval due to reasonable assurance.

DR. MORROW: Dr. Biros?

DR. BIROS: I voted for this because I think it is a safe and effective means for wound closure.

DR. MORROW: Dr. Whalen?

DR. WHALEN: I'd simply echo that.

DR. MORROW: Dr. Chang?

DR. CHANG: I voted yes because the data shows it to be efficacious and safe, and we just need the

precaution for clinicians' use in appliance.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: Approval because it's safe and effective.

DR. MORROW: Dr. Howell?

DR. HOWELL: I agree.

DR. MORROW: Dr. Witten, any further questions you have for the panel?

DR. WITTEN: No. I'd like to thank the panel and the sponsor and the audience for participating today, particularly the panel, who gives their time and effort to come here and help us review these applications.

DR. MORROW: Thank you. This meeting is now adjourned.

(Whereupon, at 12:53 p.m., the meeting was adjourned.)